pISSN 2234-1900
eISSN 2234-3156

Radiation Oncology Journal

ROJ

Vol. 38, No. 4, December 2020

www.e-roj.org

The Korean Society for Radiation Oncology

www.e-roj.org

pISSN 2234-1900
eISSN 2234-3156

ROJ Radiation Oncology Journal

Vol. 38, No. 4, December 2020

Aims and Scope

The Radiation Oncology Journal (ROJ) is an official journal of the Korean Society for Radiation Oncology. It was launched in 1983 as the official journal of the Korean Society of Therapeutic Radiology. It was changed in 2000 as the official journal of the Korean Society for Therapeutic Radiology and Oncology and finally in 2011 as ROJ.

The aims of Radiation Oncology Journal are to contribute to the advancements in the fields of radiation oncology through the scientific reviews and interchange of all of radiation oncology. It encompasses all areas of radiation oncology that impacts on the treatment of cancer using radiation as well basic experimental work relating radiation oncology and health policy. It publishes papers describing clinical radiotherapy, combined modality therapy, radiation biology, cancer biology, radiation physics, radiation informatics and new technology including particle therapy.

The ROJ is published quarterly on the last day of March, June, September, and December, one volume per year. Any physicians or researchers throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Articles in the following categories will be published: original articles, invited review articles, case reports, editorials, and letters to the editor related to basic or clinical radiation oncology. All of the manuscripts are peer-reviewed.

The ROJ is free open access journal. All articles published in ROJ are available through http://www.e-roj.org.

Open Access

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher Sung-Hwan Kim
Editor-in-Chief Won Park

Editorial office
Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine,
81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-2616 Fax: +82-2-3410-2619 E-mail: rojeditor@gmail.com

Korean Society for Radiation Oncology
Department of Radiation Oncology, St. Vincent Hospital,
93, Jungbu-daero, Paldal-gu, Suwon-si, Gyeonggi-do 16247, Republic of Korea
Tel: +82-31-881-8566 E-mail: kosro@kosro.or.kr

Printing office
M2community Co.
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-2190-7300 Fax: +82-2-2190-7333 E-mail: journal@m2community.co.kr

Published on December 31, 2020

Copyright © 2020. The Korean Society for Radiation Oncology
This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper)

ROJ Radiation Oncology Journal

Editorial Board

Publisher	Sung-Hwan Kim	*The Catholic University of Korea, ST. Vincent's Hospital*
Editor-in-Chief	Won Park	*Sungkyunkwan University, Korea*
Associate Editor	Sang Min Yoon	*University of Ulsan, Korea*
Editorial Board	Zishan Allibhai	*Southlake Regional Health Centre, Canada*
	Sevil Aliyeva Bagaturovna	*N. N. Blokhin Cancer Research Center, Russia*
	Miriam Joy C. Calaguas	*St. Luke's Medical Center, Philippines*
	Changhoon Choi	*Sungkyunkwan University, Korea*
	Hak Choy	*UT Southweastern Medical Center, USA*
	Mantana Dhanachai	*Mahidol University, Thailand*
	Keun-Yong Eom	*Seoul National University Bundang Hospital, Korea*
	Soehartati Gondhowiardjo	*University of Indonesia, Indonesia*
	Chul Soo Ha	*The University of Texas Health Science Center at San Antonio, USA*
	Ji Hong Hong	*Chang Gung Memorial Hospital, Taiwan*
	Byoung Hyuck Kim	*SMG-SNU Boramae Medical Center, Korea*
	Jin Sung Kim	*Yonsei University, Korea*
	Kyubo Kim	*Ewha Womans University, Korea*
	Tae Hyun Kim	*National Cancer Center, Korea*
	Woong Sub Koom	*Yonsei University, Korea*
	Hyung Sik Lee	*Dong-A University, Korea*
	Jong Hoon Lee	*Catholic University, Korea*
	Vedang Murthy	*Tata Memorial Centre, India*
	O Kyu Noh	*Ajou University, Korea*
	Dongryul Oh	*Sungkyunkwan University, Korea*
	Umberto Ricardi	*University of Turin, Italy*
	Vinay Sharma	*University of the Witwatersrand, South Africa*
	Tarek Shouman	*Cairo University, Egypt*
	Chang Won Song	*University of Minnesota, USA*
	Ekkasit Tharavichitkul	*Chiang Mai University, Thailand*
	Dang Huy Quoc Thinh	*HCMC Oncology Hospital, Vietnam*
	Joseph Tien-Seng Wee	*National Cancer Center, Singapore*
	Seung-Gu Yeo	*Soon Chun Hyang University, Korea*
	Zhao Chong Zeng	*Fudan Univerisity, China*
	Eduardo H. Zubizarreta	*International Atomic Energy Agency, Argentina*
Editorial Assistant	Do Hee Kim	*KOSRO, Korea*
Manuscript Editor	Ji Hye Kim	*Infolumi, Korea*

ROJ Radiation Oncology Journal

Radiat Oncol J
eISSN 2234-3156

Vol. 38, No. 4, December 2020

Review Articles

217 Erectile dysfunction and cancer: current perspective
Renu Madan, Chinna Babu Dracham, Divya Khosla, Shikha Goyal, Arun Kumar Yadav

226 Harnessing genome-wide association studies to minimize adverse radiation-induced side effects
Cecil M. Benitez, Susan J. Knox

Original Articles

Clinical Investigations

236 Post-mastectomy radiation therapy in breast reconstruction: a patterns of care study of the Korean Radiation Oncology Group
Gowoon Yang, Jee Suk Chang, Kyung Hwan Shin, Jin Ho Kim, Won Park, Haeyoung Kim, Kyubo Kim, Ik Jae Lee, Won Sup Yoon, Jihye Cha, Kyu-Chan Lee, Jin Hee Kim, Jin Hwa Choi, Sung-Ja Ahn, Boram Ha, Sun Young Lee, Dong Soo Lee, Jeongshim Lee, Sei One Shin, Yong Bae Kim

244 Prognostic significance of lymph node ratio after neoadjuvant chemoradiation therapy for esophageal squamous cell carcinoma
Jeong Yun Jang, Jesang Yu, Kye Jin Song, Yoon young Jo, Ye Jin Yoo, Sung-Bae Kim, Sook Ryun Park, Young-Hee Kim, Hyeong Ryul Kim, Jong Hoon Kim

253 Prospective evaluation of fiducial marker placement quality and toxicity in liver CyberKnife stereotactic body radiotherapy
Debnarayan Dutta, Kaushik Jagannath Kataki, Shibu George, Sruthi K. Reddy, Ajay Sashidharan, Rajesh Kannan, Ram Madhavan, Haridas Nair, Tushar Tatineni, Raghavendra Holla

262 Real world clinical outcomes of adjuvant sequential chemoradiation in patients with gallbladder carcinomas with poor performance status
Rakesh Kapoor, Kannan Periasamy, Rajesh Gupta, Arun Yadav, Divya Khosla

Physics Contribution

270 Dosimetric comparative study of 3DCRT, IMRT, VMAT, Ecomp, and Hybrid techniques for breast radiation therapy
Semaya Natalia Chen, Prabhakar Ramachandran, Pradip Deb

Copyright © 2020. The Korean Society for Radiation Oncology

ROJ Radiation Oncology Journal

Radiat Oncol J
eISSN 2234-3156

Vol. 38, No. 4, December 2020

Case Reports

282 Primary intracranial leiomyosarcoma presenting with frontal bone mass: a case report
Shaghayegh Kamian, Abdolali Ebrahimi, Kaveh Ebrahim Zadeh, Behnaz Behzadi

287 Management of grade 3 acute dermatitis with moist desquamation after adjuvant chest wall radiotherapy: a case report
Durim Delishaj, Romerai D'amico, Daniela Corvi, Giuseppe De Nobili, Alessandro Alghisi, Francesco Colangelo, Alessandra Cocchi, Fausto Declich, Carlo Pietro Soatti

Copyright ⓒ 2020. The Korean Society for Radiation Oncology

ROJ Radiation Oncology Journal

Review Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):217-225
https://doi.org/10.3857/roj.2020.00332

Erectile dysfunction and cancer: current perspective

Renu Madan[1], Chinna Babu Dracham[2], Divya Khosla[1], Shikha Goyal[1], Arun Kumar Yadav[1]

[1]*Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*
[2]*Department of Radiation Oncology, Queen's NRI Hospital, Visakhapatnam, India*

Received: June 3, 2020
Revised: July 19, 2020
Accepted: July 30, 2020

Correspondence:
Chinna Babu Dracham
Department of Radiation Oncology,
Queen's NRI Hospital,
Seethammadhara, Gurudwara lane,
Visakhapatnam 530013, India
Tel: +91-9855803437
E-mail: chinnababudraksham@gmail.com
ORCID:
https://orcid.org/0000-0002-8921-0957

Erectile dysfunction (ED) is one of the major but underreported concerns in cancer patients and survivors. It can lead to depression, lack of intimacy between the couple, and impaired quality of life. The causes of erectile dysfunction are psychological distress and endocrinal dysfunction caused by cancer itself or side effect of anticancer treatment like surgery, radiotherapy, chemotherapy and hormonal therapy. The degree of ED depends on age, pre-cancer or pre-treatment potency level, comorbidities, type of cancer and its treatment. Treatment options available for ED are various pharmacotherapies, mechanical devices, penile implants, or reconstructive surgeries. A complete evaluation of sexual functioning should be done before starting anticancer therapy. Management should be individualized and couple counseling should be an integral part of the anticancer treatment.

Keywords: Erectile dysfunction, Neoplasm, Surgery, Radiotherapy

Introduction

Cancer diagnosis and its management lead to physical and emotional distress in patients. Sexual dysfunction is one of the common problems encountered in these patients which can occur due to direct or indirect pathways. Sexual dysfunction can be in the form of erectile dysfunction (ED) and ejaculatory dysfunction such as decreased or absent semen. Chemotherapy, radiation, hormonal therapy and surgery all can lead to erectile dysfunction. ED has been widely described after prostate cancer treatment. Incidence of post-treatment ED in prostate cancer can vary from 24% (brachytherapy alone), 40% (brachytherapy plus external beam radiotherapy [EBRT]), 45% (EBRT alone), 66% (nerve-sparing radical prostatectomy [RP]), 75% (non-nerve sparing RP), and 87% for cryosurgery [1]. Recently in a population based study patient reported sexual outcome after different types of prostate cancer treatment were reported [2]. Sexual dysfunction after treatment was related to pre-treatment potency, age and type of treatment. No difference in sexual function score was noted in EBRT and brachytherapy at 2 years. Compared with EBRT alone, EBRT with androgen deprivation therapy (ADT) and RP (with or without nerve sparing) was associated with higher incidence of sexual dysfunction. Incidence of ED in cancer patients has been shown in Table 1.

Besides disease control, restoration of quality of life (QoL) is also very important due to increase number of cancer survivors. Evaluating ED using valid questionnaires and management of ED is one of the important aspects of QoL which is particularly important in developing countries where people are not comfortable discussing about their sexual issues. Age and degree of ED before the diagnosis and mode of treatment play an important role in predicting the post-treatment ED. For this review, we searched PubMed data using words "cancer related erectile dysfunction", "erectile dysfunction in cancer", "sexual dysfunction in genitourinary malignancies," and "psychosocial outcome of cancer survivors". All studies reporting erectile dysfunction in cancer patients and survivors were reviewed. Around 60 studies were screened and data from 54 studies that reported sexual dysfunction or erectile dysfunction in cancer was included in the review.

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. Erectile dysfunction in cancer (original)

S. No.	Study	Year	No. of patients	Age (yr)	Primary tumor	Treatment modality (% of patients)	RT dose (Gy)	Probability of sexual function preservation	Incidence of ED	Remarks
1	Mullins et al. [2]	2019	835	63.7 (mean)	Prostate	EBRT (23%) Brachytherapy (15%) EBRT + ADT (12%) RP + NS (41%) RP + non-NS (10%)	-	EBRT (14%–70%) Brachytherapy (14%–70%) EBRT + ADT (8%–52%) RP + NS (4.7%–45.3%) RP + non-NS (5%–34%)	-	RT alone results in the best preservation of sexual function
2	Resnick et al. [8]	2013	1655	55–94	Prostate	Prostatectomy (70.3%) EBRT (29.6%)	-	-	Prostatectomy (46.7%) EBRT (39.7%)	Patients underwent prostatectomy were more likely to have erectile dysfunction at 2 years and 5 years
3	Hekal et al. [12]	2011	45	31–64	Urinary bladder	RC + NS (46.6%) RC + non-NS (53.4%)	-	RC + NS (spontaneous erection, 57.8%) RC + non-NS (no spontaneous erection)	RC + NS (42.2%) RC + non-NS (100%)	Gradual progressive improvement was observed in vasogenic competence in NS cases
4	Zippe et al. [13]	2004	49	57.8 (mean)	Urinary bladder	RC + NS (33%) RC + non-NS (67%)	-	RC + NS (spontaneous erection, 50%) RC + non-NS (spontaneous erection, 3%)	RC + NS (50%) RC + non-NS (97%)	-
5	Loh-Doyle et al. [14]	2020	151	66.1 (median)	Urinary bladder	RC (100%)	-	-	Loss of penile length, ≥2.54 cm (55.1%)	RC can result in significant sexual dysfunction, as the significant loss in penile length
6	Tal et al. [20]	2014	76	29 (mean)	Testicular cancer	Orchiectomy (100%) EBRT (26.3%) Chemotherapy (47.3%) RPLND (19.7%)	-	-	Loss of ability to maintain erection (84%)	ED after treatment appear to have normal erectile haemodynamics on penile duplex Doppler and all responded to treatment
7	Capogrosso et al. [21]	2016	143	42 (median)	Testicular cancer	Orchiectomy (100%) EBRT (32.9%) Chemotherapy (81.8%) RPLND (42.8%)	20–24	-	24.5%	Adjuvant therapy was not associated with impaired recovery of normal sexuality
8	Duran et al. [22]	2015	56	27–79	Rectum	APR (19.6%) LAR (80.4%) RT (80.4%)	-	-	21.8%	Lower 1/3 of tumor location, age younger than 60 years, RT, and stoma were risk factors for ED
9	Pokharel et al. [25]	2019	26	26–75	Colorectal	NACRT (100%) APR (7.6%) LAR (92.3%)	-	Sexual desire (57.7%)	ED (42.3%) Not able to attain erection (38.4%) Unable to ejaculate (34.6%)	-
10	van der Wielen et al. [27]	2007	268	68 (median)	Prostate	EBRT; standard vs. dose escalation 3DCRT in both arms	68 vs. 78	Sexual desire (41%)	38%	In sexual function, no significant differences were found between the two dose-arms

(Continued to the next page)

https://doi.org/10.3857/roj.2020.00332

https://doi.org/10.3857/roj.2020.00332

Table 1. Continued

S. No.	Study	Year	No. of patients	Age (yr)	Primary tumor	Treatment modality (% of patients)	RT dose (Gy)	Probability of sexual function preservation	Incidence of ED	Remarks
11	Pinkawa et al. [31]	2011	156	55–83	Prostate	EBRT (3DCRT vs. IMRT)	70 vs. 76	Patients with erections firm enough for sexual intercourse; 32% vs. 65%	86% vs. 70%	Dose escalation with IMRT is not associated with increased sexual morbidity
12	Mangar et al. [33]	2006	51	47–78	Prostate	EBRT; standard vs. dose escalation Conformal RT	64 vs. 74	Remained potent (23.5%) Reduced potency (43.1%) Impotent (33.3%)	78%	Penile bulb dose; D_{90} > 50 Gy significant risk of erectile dysfunction
13	Fisch et al. [34]	2001	21	72 (mean)	Prostate	EBRT; 3DCRT	67.3–87.3	Remained potent (38%) Reduced potency (38%) Impotent (24%)	62%	70 Gy to more than 70% volume of penile bulb, high risk of ED
14	Bruner et al. [36]	2015	1006	50–88	Prostate	EBRT (3DCRT vs. IMRT)	79.2 vs. 79.2	No statistically significance differences were observed between two groups in erectile function scores	-	Penile bulb dose does not correlate with ED
15	Thor et al. [38]	2015	501	-	Prostate	EBRT; 3DCRT (60.2%) RP + 3DCRT (39.8)	70	Suggested that presence of naturally occurring erections were crucial for erectile and orgasmic function	41%	Strong association found between ED and doses to total penile structure than penile bulb
16	Zelefsky et al. [53]	2006	561	≥60	Prostate	EBRT; ADT + IMRT vs. IMRT	81	Sexual desire (51%)	ADT +IMRT (57%) IMRT alone (43%)	Addition of short-term ADT significantly increased the risk of ED in these patients
17	Pinkawa et al. [54]	2009	123	53–84	Prostate	EBRT ± PDE-5i	70.2–72	Ability to have an erection (70%) Erections firm enough for sexual intercourse (53%)	30%	Age and diabetes are risk factors for post EBRT ED

RT, radiotherapy; ED, erectile dysfunction; EBRT, external beam radiotherapy; ADT, androgen deprivation therapy; RP, radical prostatectomy; NS, nerve sparing; RC, radical cystectomy; RPLND, retroperitoneal lymph node dissection; APR, abdominoperineal resection; LAR, low anterior resection; NACRT, neoadjuvant chemoradiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PDE-5i, phosphodiesterase 5 inhibitors.

1. Psychological and emotional impact of ED

The loss of erectile ability leads to depressive symptoms, lack of sexual satisfaction and general happiness in life. Men who fail to achieve erection tend to lose confidence [3]. Depression and sexual avoidance in turn can affect the intimacy level and relationship of the couple. Studies have reported that ED after curative treatment is one of the common causes of depression in prostate cancer patients.

2. Mechanism of penile erection

Blood supply to the penis occurs via branches of external and internal pudendal arteries. Penile innervations are derived from pudendal and cavernous nerves. Pudendal nerve is responsible for somatic motor and sensory nerve supply. Cavernous nerve is a part of autonomic nervous systems and includes sympathetic and parasympathetic fibres. It runs in crus and corpora of the penis and regulates the blood flow during erection and flaccid state [4].

An erection begins with sensory and mental stimulation. Sexual arousal leads to relaxation of smooth muscles of the penile arteries which increases the blood flow to penis. This leads to rigidity and thus erection of the penis. While returning to flaccid state, penile muscles contract and increase the venous outflow and decrease the length and girth of the penis. The ability to attain and sustain erection depends on integrity of vascular supply and nerve supply.

Causes of ED in Cancer

Causes of ED in cancer patient are follows: (1) emotional, physical and financial stress; (2) pain, anxiety and disturbed body image; (3) damage to penile nerve and vessels during surgery, radiotherapy (RT) and chemotherapy; (4) ADT; (5) penectomy for cancer penis; Nitric oxide (NO) pathway plays an important role in achieving erection. NO is the principle agent responsible for relaxation of penile smooth muscles and thus erection. Radiation leads to damage and inflammation of cavernous nerves, leading to decreased production of nitric oxide synthase and NO which subsequently leads to ED [5]; Fibrotic changes in blood vessels and atrophy of corpora cavernosa due to surgery and RT lead to reduced blood flow in erectile chamber, making it less expansile for blood accumulation during erection.

1. ED in surgery

Prostate cancer is one of the most common cancers in males worldwide. Due to widespread use of prostate-specific antigen (PSA), increased numbers of young and healthy men are diagnosed with prostate cancer as compared to past. RP leads to excellent survival and is one of the established treatments for early stage prostate cancer. With excellent disease control, potential side effects of surgery are a growing concern out of which ED is one of the important focuses [6]. Wide range of ED (14%–90%) has been reported after RP due to methodological differences in various studies [7]. Resnick et al. [8] published data from the Prostate Cancer Outcomes Study (PCOS) comprising of 1,164 patients who underwent prostatectomy and 491 patients who received RT. These patients were followed up for 15 years. Incidence of ED at 2 years (78.8% vs. 60.8%) and 5 years (75.7% vs. 71.9%) was higher in surgery as compared to RT. However, the difference was not significant at 15 years. It has been thought that new surgery techniques, i.e., robotic surgery may reduce other side effects, its role in reducing ED is not clear. Nerve sparing surgery in prostate cancer may reduce the incidence of ED. Despite the sparing of cavernous nerve in most of the prostate surgery, it tends to get some sort of bruising and trauma during the surgery which can take up to 2 years to heal. During this time period, men may have difficulty in achieving natural erection which can lead to degeneration of penile tissue and structural alterations [9]. Thus only 9%–40% patients resume their sexual function after surgery [10,11]. Hekal et al. [12] noted veno-occlusive dysfunction after nerve sparing and non-nerve sparing surgery, which was significantly improved 1 year after nerve-sparing group and spontaneous erections returned after 12 months.

ED can be commonly seen after surgery for bladder cancer. Zippe et al. [13] followed 49 preoperatively sexually active men for 47 months who underwent radical cystectomy (RC) for bladder cancer. At least some degree of ED was found in 86% of the patients after surgery.

Perception of reduced penile length has been seen after RP and RC. Loh-Doyle et al. [14] analysed sexual function in 151 patients who underwent RC for bladder cancer and observed that 55% patients perceived loss in penile length and out of the 55% patients, approximately half of them reported a shortening of 1 inch or more. Erectile dysfunction has also been seen after transurethral resection of bladder tumor (TURBT) and after urinary diversion procedure due to presence of a stoma and sense of disturbed body image [15]. Surgery for penile cancer can also significantly jeopardise sexual function. Scarberry et al. [16] found that after partial penectomy half of the patients can still have normal erection. Gulino et al. [17] reported that after 6 months of conservative surgery (glansectomy) for localized penile cancer, 73% had spontaneous rigid erections.

Testicular cancer is commonly seen in young patients and thus determining sexual function is even more important. After treatment of testicular cancer, 12%–40% of patients can have ED due to hormonal imbalance including low testosterone, orchidectomy

 https://doi.org/10.3857/roj.2020.00332

or retroperitoneal lymph node dissection [18,19]. Tal et al. [20] reported that 84% patients had loss of sustained erection after treatment although 24% patients had transient ED even before the diagnosis. In one study it was found that out of every four patients, one patient develops ED, out of which 10% will have severe ED [21].

Colorectal cancer (CRC) is another common malignancy in males. Surgery for these cancers may also impair sexual function due to hypogastric and autonomic nerve injury [22]. After CRC surgery, sexual dysfunction can range from 10% to 50%, depending on the assessments used [23,24]. In one study, 18% patients had decreased ejaculation and erection after abdomino-pelvic resection (APR) or low anterior resection (LAR) [22]. A recent study observed that 11 out of 20 patients (42.3%) had sexual dysfunction after APR/LAR for colorectal cancer [25].

2. Radiotherapy-induced ED

Radiotherapy-induced erectile dysfunction (RIED) occurs due to higher dose to penile bulb, crura and neurovascular bundle especially in bladder and prostate cancer. Incidence of RIED has been mentioned above. RIED generally take over 1 year to develop, gradually increases and becomes constant after 3 years [26]. It depends on pre-treatment potency level, RT dose to the penile bulb and use of other concomitant treatment modalities. In a dose escalation study of prostate cancer, incidence of newly diagnosed ED was reported as 36% and 38% at 2 and 3 years post-RT [27]. Recent studies have shown that approximately 30%–40% patients develop ED after RT [26] as compared to 60%–70% in earlier studies [28]. In one study, ejaculatory disturbance (decreased or absent semen, pain during ejaculation and hemospermia) have been reported in 2%–56% after RT while dissatisfaction with sex life can vary from 25% to 60% and lack of sexual desire can vary from 12% to 58% of the patients with prostate cancer patients after RT [28]. Decreased intensity of orgasm has also been reported. In one study of 262 prostate cancer patients of age ≤60 years, 73% patients reported either no or only minimal decline in ED after 2 years of RT as compared to baseline [29]. Over the past few years, there has been decrease in the incidence of adverse effects of RT including ED due to increased use of brachytherapy as compared to the past [30] and newer and sophisticated RT techniques like intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and proton therapy although data is insufficient pertinent to ED. In one study, it was reported that sexual function was more retained at 1 year in IMRT arm (30%) as compared to three-dimensional conformal radiotherapy (3DCRT) arm (14%) [31]. Siglin et al. [26] showed that decline in sexual function occur maximum after 2 years of RT and then starts stabilising and occasionally can return to baseline.

3. Radiotherapy dose

Till date, there is no definite data to suggest the co-relation of RT dose and ED. Relating ED to RT alone is difficult as multiple other factors also contribute to ED like smoking, diabetes mellitus, hypertension, concomitant treatment, etc. Earlier in a study by RTOG group, Roach et al. [32] observed that median penile bulb dose of >52.5 Gy is responsible for high risk of ED. In a dose escalation study for prostate cancer, Mangar et al. [33] reported that risk of impotency was significant higher in those whom penile bulb received 50 Gy or more dose of RT.

Few studies have observed that ED and penile bulb dose show a dose volume relationship. Fisch et al. [34] reported ED in 0%, 80%, and 100% of patients when dose received by 70% of penile bulb volume (D_{70}) was 0–40 Gy, 40–70 Gy, and >70 Gy, respectively. Similarly, Mangar et al. [33] observed that if the dose received by 90% of penile bulb volume (D_{90}) is 50 Gy or more, it significantly increases the risk of ED. Wernicke et al. [35] reported that dose received by 30%, 45%, 60%, and 75% volume of penile bulb (D_{30}, D_{45}, D_{60}, and D_{75}, respectively) are also important parameters to define the risk of ED.

QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) has defined that penile bulb may not be a critical structure for ED but may act as surrogate for yet to identified critical structures for ED and suggested a mean dose of not more than 50 Gy to 95% volume of penile bulb. In a recently published preliminary patient reported outcomes in RTOG 0126 trial, at 2 years, no significant difference in sexual function was reported in 3DCRT (high penile bulb dose) or IMRT (lower penile bulb dose) arm [36]. However It is recommended that mean RT dose to penile bulb should be kept <50 Gy and it is important to limit the D_{70} to 70 Gy and D_{90} to 50 Gy [37].

Based on the patient reported outcomes, Thor et al. [38] identified three domains of sexual dysfunction in males after radiotherapy for prostate cancer, namely ED, orgasmic dysfunction, and pain. He studied the involvement of various penile structures by radiotherapy in ED and observed that other than penile bulb, RT dose to corpora cavernosa (CC) and total penile structure is also important to maintain intact erectile function.

4. Chemotherapy and hormonal therapy

Chemotherapy and hormone therapy also play a role in ED. Several chemotherapeutic agents are known to cause ED by causing neural and vasculature damage. These are mainly cisplatin, vincristin and vinblastin. Wiechno et al. [19] found that out of 269 men with testicular cancer, 40%, developed ED after platinum based chemotherapy. Similarly 20.8% (out of 202 men) patients with testicular cancer developed ED after platinum based chemotherapy [39]. ED

has been also observed after high-dose chemotherapy with melphalan, cyclophosphamide or etoposide along with total body radiotherapy in haematological malignancies [40].

ADT is commonly used in the treatment of prostate cancer which is known to cause lack of sexual interest. Loss of libido usually develops within the first several months, and ED follows. In one study sexual inactivity started 6 months after starting ADT [41]. Couples should be counselled before ADT is started. Recovery of erectile function is possible after discontinuation of short-term ADT. However, recovery may be delayed or incomplete [42]. One study has reported that prostate cancer patients who received ADT, are 23% more likely to develop depression due to ED [43].

Management of ED

Age of patient and his sexual partner is one of the most important factors while deciding the treatment plan.

1. Oral and injectable pharmacotherapy

Phosphodiesterase-5 inhibitors (PDE-5i)/sildenafil citrate (Viagra) is highly an effective and most commonly used oral agent as a first line therapy used in clinical practice [44]. Injury during surgery may lead to hypoxia in penile tissue. PDE-5i increase the release of NO resulting in smooth muscle relaxation and increased blood flow in corpus cavernosum. Sildenafil has an onset of action time, approximately 30 minutes to 1 hour. Cavernous nerve initiates the required erectile pathway so that PDE-5i can be effective. Thus, the effectiveness of these drugs is limited by severity of cavernous nerve injury. Although PDE-5i is the first line treatment for ED, 30%–40% patients do exhibit little or no response to it [45]. Prophylactic role of sildenafil citrate in prostate cancer patients was shown by Zelefsky et al. [46]. Patients were randomized to receive either sildenafil daily 50 mg or placebo during and 6 months after RT. In sildenafil arm, significant improvement in ED was noted at 6, 12, and 24 months [46]. Common side effects of sildenafil are headache, facial flushing, stuffy nose and gastrointestinal upset. PDE-5i use is contraindicated in patients taking nitrates for chest pain. It should be used carefully in those who are on alpha-blockers.

Alprostadil (synthetic form of prostaglandin E1 [PGE1]), phentolamine (vasodilator) or papaverine (smooth muscle dilator) can be used for intracavernosal injection [47]. Combination of the drugs is used if one drug fails. As it is a relatively invasive procedure for the patients, it is generally used as a second line therapy in well counselled and motivated patients once treatment becomes refractory to oral agents. Side effects are related to injection site pain and fibrosis.

2. Intraurethral PGE1

Alprostadil (MUSE) suppository is inserted in urethra via a small applicator. It creates a vaso-dilatory effect on penile blood vessels and thus helps in penile erection [48].

3. Vacuum erection device

It is a battery powered device and can be used in conjunction with a PDE-5i to help maintain and sustain an erection. It consists of cylinder with a pump and constriction ring. Cylinder and pump create vacuum that helps in penile erection while constriction ring helps in maintain erection. Although it is an inexpensive approach, mechanical failure is a problem. Other problems with this device are infection and penile discomfort.

4. Penile prosthesis implants

Inflatable or non-inflatable penile implants is an effective safe and durable treatment option for ED and are generally used once patient becomes refractory to other treatment options. In one study it was reported that only $<5\%$ men underwent penile implantation after RP [49]. Wilson et al. [50] found that 10- and 15-year revision-free survival was 68.9% and 59.7%, respectively after first time implant.

5. Vascular reconstruction

Vascular reconstruction in the form of arterial vascularisation, venous arterialization or venous stripping improves blood flow to corpora cavernosa and thus helps in achieving and maintaining erection [51]. This procedure is generally reserved for those who do not respond to oral or injectable pharmacological therapy.

6. Low-intensity extracorporeal shock wave therapy

It is a non-invasive newer technology for the treatment of ED. It acts by inducing localized angiogenesis, and pushing blood to the penis [52]. It is safe and can be used in men with failed medical therapy.

Conclusion

Cancer diagnosis and its treatment can lead to variable degree of sexual dysfunction in patients ranging from loss of libido to complete loss of erection. As sexual issue is a generally less discussed topic, ED is one of the underreported issues in cancer patients. ED can lead to depression and impaired quality of life. Thus, it is very important to evaluate ED before and after treatment. For men who have ED or in those when ED is predictable, couple counselling should be an essential component of the cancer management. Method of sexual rehabilitation should be individualised for each patient.

https://doi.org/10.3857/roj.2020.00332

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Robinson JW, Moritz S, Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. Int J Radiat Oncol Biol Phys 2002;54:1063-8.
2. Mullins BT, Basak R, Broughman JR, Chen RC. Patient-reported sexual quality of life after different types of radical prostatectomy and radiotherapy: analysis of a population-based prospective cohort. Cancer 2019;125:3657-65.
3. Nelson CJ, Mulhall JP, Roth AJ. The association between erectile dysfunction and depressive symptoms in men treated for prostate cancer. J Sex Med 2011;8:560-6.
4. Andersson KE. Erectile physiological and pathophysiological pathways involved in erectile dysfunction. J Urol 2003;170(2 Pt 2):S6-14.
5. Mahmood J, Shamah AA, Creed TM, et al. Radiation-induced erectile dysfunction: recent advances and future directions. Adv Radiat Oncol 2016;1:161-9.
6. Liu C, Lopez DS, Chen M, Wang R. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. J Sex Med 2017;14:1496-503.
7. Tal R, Alphs HH, Krebs P, Nelson CJ, Mulhall JP. Erectile function recovery rate after radical prostatectomy: a meta-analysis. J Sex Med 2009;6:2538-46.
8. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013;368:436-45.
9. Mulhall J, Land S, Parker M, Waters WB, Flanigan RC. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med 2005;2:532-42.
10. Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. J Urol 1999;162(3 Pt 1):722-5.
11. Mahjoubi B, Mirzaei R, Azizi R, Jafarinia M, Zahedi-Shoolami L. A cross-sectional survey of quality of life in colostomates: a report from Iran. Health Qual Life Outcomes 2012;10:136.
12. Hekal IA, Mosbah A, El-Bahnasawy MS, El-Assmy A, Shaaban A. Penile haemodynamic changes in post-radical cystectomy patients. Int J Androl 2011;34:27-32.
13. Zippe CD, Raina R, Massanyi EZ, et al. Sexual function after male radical cystectomy in a sexually active population. Urology 2004;64:682-6.
14. Loh-Doyle JC, Han J, Ghodoussipour S. Factors associated with patient-reported penile length loss after radical cystoprostatectomy in male patients with bladder cancer. J Sex Med 2020;17:957-63.
15. Krajewski W, Halska U, Poletajew S, et al. Influence of transurethral resection of bladder cancer on sexual function, anxiety, and depression. Adv Exp Med Biol 2018;1116:37-50.
16. Scarberry K, Angermeier KW, Montague D, Campbell S, Wood HM. Outcomes for organ-preserving surgery for penile cancer. Sex Med 2015;3:62-6.
17. Gulino G, Sasso F, Palermo G, et al. Sexual outcomes after organ potency-sparing surgery and glans reconstruction in patients with penile carcinoma. Indian J Urol 2013;29:119-23.
18. Rossen P, Pedersen AF, Zachariae R, von der Maase H. Sexuality and body image in long-term survivors of testicular cancer. Eur J Cancer 2012;48:571-8.
19. Wiechno P, Demkow T, Kubiak K, Sadowska M, Kaminska J. The quality of life and hormonal disturbances in testicular cancer survivors in Cisplatin era. Eur Urol 2007;52:1448-54.
20. Tal R, Stember DS, Logmanieh N, Narus J, Mulhall JP. Erectile dysfunction in men treated for testicular cancer. BJU Int 2014;113:907-10.
21. Capogrosso P, Boeri L, Ferrari M, et al. Long-term recovery of normal sexual function in testicular cancer survivors. Asian J Androl 2016;18:85-9.
22. Duran E, Tanriseven M, Ersoz N, et al. Urinary and sexual dysfunction rates and risk factors following rectal cancer surgery. Int J Colorectal Dis 2015;30:1547-55.
23. Eveno C, Lamblin A, Mariette C, Pocard M. Sexual and urinary dysfunction after proctectomy for rectal cancer. J Visc Surg 2010;147:e21-30.
24. Lange MM, van de Velde CJ. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol 2011;8:51-7.
25. Pokharel N, Katwal G, Adhikari SK. Incidence of the bowel, bladder, and sexual dysfunction following surgery for colorectal malignancy. J Nepal Health Res Counc 2019;17:262-7.
26. Siglin J, Kubicek GJ, Leiby B, Valicenti RK. Time of decline in sexual function after external beam radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;76:31-5.
27. van der Wielen GJ, van Putten WL, Incrocci L. Sexual function after three-dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. Int J Radiat Oncol Biol Phys 2007;68:479-84.
28. Incrocci L, Slob AK, Levendag PC. Sexual (dys)function after radiotherapy for prostate cancer: a review. Int J Radiat Oncol Biol Phys 2002;52:681-93.

29. Hoppe BS, Nichols RC, Henderson RH, et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. Cancer 2012;118:4619-26.
30. Challapalli A, Jones E, Harvey C, Hellawell GO, Mangar SA. High dose rate prostate brachytherapy: an overview of the rationale, experience and emerging applications in the treatment of prostate cancer. Br J Radiol 2012;85 Spec No 1(Spec Iss 1):S18-27.
31. Pinkawa M, Piroth MD, Holy R, et al. Combination of dose escalation with technological advances (intensity-modulated and image-guided radiotherapy) is not associated with increased morbidity for patients with prostate cancer. Strahlenther Onkol 2011;187:479-84.
32. Roach M, Winter K, Michalski JM, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. Int J Radiat Oncol Biol Phys 2004;60:1351-6.
33. Mangar SA, Sydes MR, Tucker HL, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). Radiother Oncol 2006;80:355-62.
34. Fisch BM, Pickett B, Weinberg V, Roach M. Dose of radiation received by the bulb of the penis correlates with risk of impotence after three-dimensional conformal radiotherapy for prostate cancer. Urology 2001;57:955-9.
35. Wernicke AG, Valicenti R, Dieva K, Houser C, Pequignot E. Radiation dose delivered to the proximal penis as a predictor of the risk of erectile dysfunction after three-dimensional conformal radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2004;60:1357-63.
36. Bruner DW, Hunt D, Michalski JM, et al. Preliminary patient-reported outcomes analysis of 3-dimensional radiation therapy versus intensity-modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group (RTOG) 0126 prostate cancer trial. Cancer 2015;121:2422-30.
37. Roach M 3rd, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation dose-volume effects and the penile bulb. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S130-4.
38. Thor M, Olsson CE, Oh JH, et al. Radiation dose to the penile structures and patient-reported sexual dysfunction in long-term prostate cancer survivors. J Sex Med 2015;12:2388-97.
39. Bumbasirevic U, Bojanic N, Pekmezovic T, et al. Health-related quality of life, depression, and sexual function in testicular cancer survivors in a developing country: a Serbian experience. Support Care Cancer 2013;21:757-63.
40. Chatterjee R, Andrews HO, McGarrigle HH, et al. Cavernosal arterial insufficiency is a major component of erectile dysfunction in some recipients of high-dose chemotherapy/chemo-radiotherapy for haematological malignancies. Bone Marrow Transplant 2000;25:1185-9.
41. Walker LM, Santos-Iglesias P, Robinson J. Mood, sexuality, and relational intimacy after starting androgen deprivation therapy: implications for couples. Support Care Cancer 2018;26:3835-42.
42. Li R, Ruckle HC, Schlaifer AE, El-Shafei A, Yu C, Jones JS. The effect of androgen deprivation therapy before salvage whole-gland cryoablation after primary radiation failure in prostate cancer treatment. Urology 2015;85:1137-42.
43. Klaassen Z, Arora K, Wilson SN, et al. Decreasing suicide risk among patients with prostate cancer: implications for depression, erectile dysfunction, and suicidal ideation screening. Urol Oncol 2018;36:60-6.
44. Albaugh JA. Addressing and managing erectile dysfunction after prostatectomy for prostate cancer. Urol Nurs 2010;30:167-177.
45. Munk NE, Knudsen JS, Comerma-Steffensen S, Simonsen U. Systematic review of oral combination therapy for erectile dysfunction when phosphodiesterase type 5 inhibitor monotherapy fails. Sex Med Rev 2019;7:430-41.
46. Zelefsky MJ, Shasha D, Branco RD, et al. Prophylactic sildenafil citrate improves select aspects of sexual function in men treated with radiotherapy for prostate cancer. J Urol 2014;192:868-74.
47. Duncan C, Omran GJ, Teh J, Davis NF, Bolton DM, Lawrentschuk N. Erectile dysfunction: a global review of intracavernosal injectables. World J Urol 2019;37:1007-14.
48. Voznesensky M, Annam K, Kreder KJ. Understanding and managing erectile dysfunction in patients treated for cancer. J Oncol Pract 2016;12:297-304.
49. Bajic P, Patel PM, Nelson MH, et al. Penile prosthesis implantation and timing disparities after radical prostatectomy: results from a statewide claims database. J Sex Med 2020;17:1175-81.
50. Wilson SK, Delk JR, Salem EA, Cleves MA. Long-term survival of inflatable penile prostheses: single surgical group experience with 2,384 first-time implants spanning two decades. J Sex Med 2007;4(4 Pt 1):1074-9.
51. Molodysky E, Liu SP, Huang SJ, Hsu GL. Penile vascular surgery for treating erectile dysfunction: current role and future direction. Arab J Urol 2013;11:254-66.
52. Chung E. Penile prosthesis implant: scientific advances and technological innovations over the last four decades. Transl Androl Urol 2017;6:37-45.
53. Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM, Amols H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J

Urol 2006;176(4 Pt 1):1415-9.
54. Pinkawa M, Gagel B, Piroth MD, et al. Erectile dysfunction after external beam radiotherapy for prostate cancer. Eur Urol 2009;55:227-34.

ROJ Radiation Oncology Journal

Review Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):226-235
https://doi.org/10.3857/roj.2020.00556

Harnessing genome-wide association studies to minimize adverse radiation-induced side effects

Cecil M. Benitez, Susan J. Knox

Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, CA, USA

Received: July 31, 2020
Revised: September 20, 2020
Accepted: September 22, 2020

Correspondence:
Susan J. Knox
Department of Radiation Oncology, Stanford University School of Medicine, Palo Alto, CA 94304, USA.
Tel: +1-650-725-2720
Fax: +1-650-723-7254
E-mail: sknox@stanford.edu
ORCID:
https://orcid.org/0000-0003-1377-637X

Radiotherapy is used as definitive treatment in approximately two-thirds of all cancers. However, like any treatment, radiation has significant acute and long-term side effects including secondary malignancies. Even when similar radiation parameters are used, 5%–10% of patients will experience adverse radiation side effects. Genomic susceptibility is thought to be responsible for approximately 40% of the clinical variability observed. In the era of precision medicine, the link between genetic susceptibility and radiation-induced side effects is further strengthening. Genome-wide association studies (GWAS) have begun to identify single-nucleotide polymorphisms (SNPs) attributed to overall and tissue-specific toxicity following radiation for treatment of breast cancer, prostate cancer, and other cancers. Here, we review the use of GWAS in identifying polymorphisms that are predictive of acute and long-term radiation-induced side effects with a focus on chest, pelvic, and head-and-neck irradiation. Integration of GWAS with "omic" data, patient characteristics, and clinical correlates into predictive models could decrease radiation-induced side effects while increasing therapeutic efficacy.

Keywords: Radiogenomics, Radiation-induced side effects, Genome-wide association study (GWAS), Normal tissue toxicity, Radiotherapy

Introduction

Radiation therapy (also called radiotherapy) is a localized cancer treatment that targets cancer cells with high doses of radiation. More than half of patients with cancer, including children with cancer, will be treated with radiotherapy [1]. Acute radiation-induced side effects include dermatitis and fatigue, while long-term side effects include increased risk for secondary malignancies. Site-specific acute side effects such as mucositis, esophagitis, and enteritis, may develop when treating head and neck cancers, lung cancers, and gastrointestinal (GI) cancers, respectively. Patients treated for breast cancer and lung cancer may also develop irreversible cardiotoxicity and pulmonary fibrosis after thoracic irradiation [2,3]. Normal tissue toxicity determines the maximum radiation dose delivered to tumors. To increase the therapeutic ratio of radiation, radiation oncologist and their teams individualize patient's treatment plans by selecting the appropriate treatment modality, radiation dose, fractionation, and target volumes. Recent phase II–III clinical trials have focused on comparing treatment modalities such as ultra-hypofractionation versus conventionally fractionated therapy, and reducing effective doses to decrease acute and long-term side effects [4,5]. Despite this customization, 10%–20% of patients receiving radiotherapy develop grade 2 toxicity and 2%–5% develop grade 3 toxicity [6,7]. Genetic variability, in part, explains this clinical variability.

It is estimated that genetic variability may account for approximately 40% of the variability seen in treatment side effects, while lifestyle risk factors, not limited to obesity, smoking and drinking, account approximately for 60% of the variability [8–10]. Single nucleotide polymorphisms (SNPs), gene deletions, epigenetic differ-

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ences and differential gene expression are markers of genetic variability. Genome-wide association studies (GWAS) use an agnostic approach to identify SNPs associated with a predetermined outcome such as normal tissue toxicity. Though the majority of GWAS have focused on polymorphisms that increase the risk of developing primary cancers and tumor radiosensitivity, there is evidence that polymorphisms that increase the risk of radiation-induced cancers differ from those that increase the risk of primary cancers [11,12]. Therefore, genetic markers of normal tissue toxicity secondary to radiation are needed to further personalize treatments and improve outcomes.

Historically, genes that increase normal tissue toxicity following radiation were discovered through studies of rare monogenetic diseases such as Li-Fraumeni syndrome, retinoblastoma, neurofibromatosis type 1, ataxia telangiectasia, and Fanconi's anemia. These diseases not only raised the knowledge about genetic predisposition of normal tissue toxicity, but also provided a biological framework for future discoveries, such as those informed by candidate gene approaches [13]. Candidate gene approaches further identified polymorphisms associated with genes involved in DNA repair, oxidation, and cytokine synthesis that increase the risk for radiation-induced side effects [7]. The development of SNP microarrays paved the way for non-priori identification of additional polymorphisms through GWAS approaches. To increase the power that is needed to identify polygenic causes of radiotoxicity, establishment of the Radiogenomics Consortium promoted pooling of GWAS data and standardization in reporting GWAS and radiation-induced side effects [14,15]. Now, meta-analysis of aggregate GWAS and whole-genome sequencing continue to promote new discoveries in the field of radiogenomics.

To bookmark the progress of GWAS in elucidating polymorphisms contributing to normal tissue toxicity following radiation, we compiled a narrative review. We focused on seminal literature spanning from 2010 to 2020. Search terms such as polymorphisms, GWAS, radiation, radiotherapy, radiosensitivity, normal tissue toxicity, and radiation effects were queried through PubMed, Google Scholar, and SearchWorks. This review focuses on radiation-induced side effects after chest, pelvic, and head-and-neck irradiation based on data availability. We include both early and late side effects including the risk for secondary cancers. We do not review GWAS identifying polymorphisms affecting development of primary cancers, recurrence, mortality, and tumor radiosensitivity. The GWAS described in this review focus on germline polymorphisms. We hope that early identification of patients that are at high risk for radiation-induced side effects could help to further personalize patients' treatment plans, including the choice of modality, radiation dose and fractionation schedules. Fig. 1 provides an overview of the GWAS workflow. Table 1 summarizes the GWAS literature presented in this article.

Chest Irradiation

Chest-irradiation puts the breasts, heart, lungs, esophagus, and major blood vessels at risk for toxicity [16,17]. Candidate gene approaches have identified polymorphisms involved in DNA repair pathways related to skin toxicity, pneumonitis, and esophageal toxicity [18–23]. Few studies have used a GWAS approach to discover polymorphisms associated with radiation-induced toxicity. Bourgier et al. [24] attempted to identify polymorphisms influencing late radiation-induced subcutaneous fibrosis, radiation-induced lymphocyte apopto-

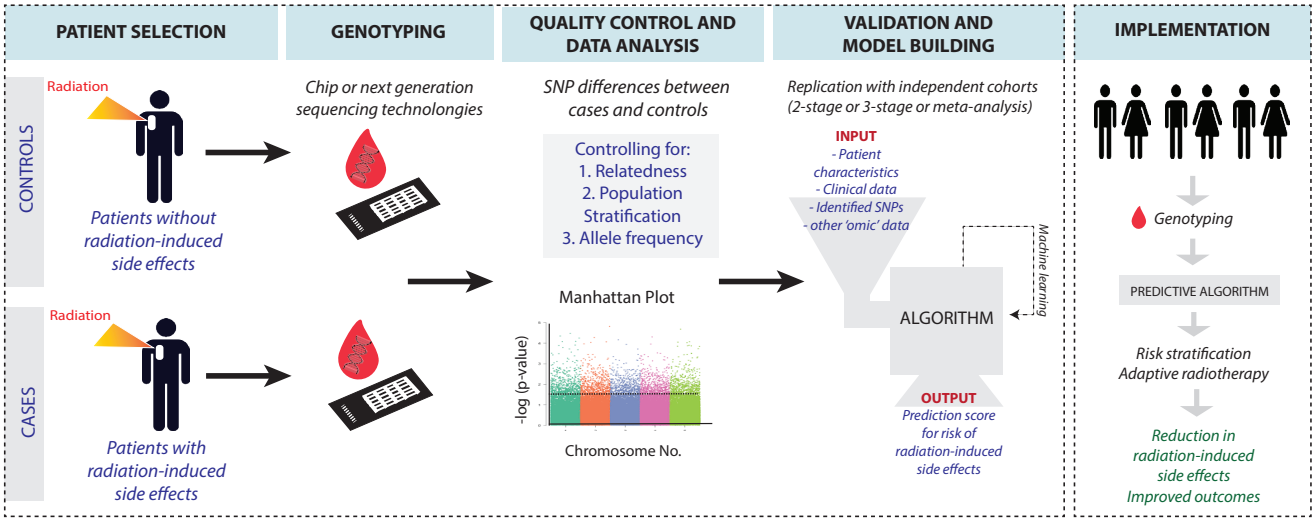


Fig. 1. Schematic identifying genetic variants and their potential to inform cancer treatments.

Table 1. Summary of genome-wide association studies (GWAS) and significant polymorphisms

Study, year	Study type	Race/ethnic group (sample number)	Cancer type (staging)	RT technique, dose, fractionation	Genotyping technology	Effect and scoring system	Significant polymorphisms (gene; OR/RR)	Model incorporation
Kerns et al. [33], 2010	Discovery GWAS	African-American (N = 138)	Prostate cancer (stage II, III, IV)	3D conformal or IMRT 39–42 fx of 1.8 Gy/fx	Affymetrix 6.0 array	Erectile dysfunction based on SHIM questionnaire	rs2268363 (*FSHR*; OR = 7.03), rs10194115 (*TTC7A*; OR = 9.0), rs2806864 (*PTGFRN*; OR = 6.42), rs10861905 (*CMKLR1*; OR = 33.95)	Yes
Kerns et al. [35], 2013	2-stage GWAS	75% European descent, 25% African/Hispanic American/Asian (Ndis = 346, Nrep = 377)	Prostate cancer (stage T1, T2, T3)	Brachytherapy (TG43 or palladium) ± EBRT (3D or IMRT to 24–50 Gy), 2 Gy/fx	Affymetrix 6.0 array	Urinary straining scored with AUASS	rs17779457 (MOB3B; beta = 2.4), rs13035033 (*MYO3B*; beta = 0.9)	No
Kerns et al. [34], 2013	2-stage GWAS	79% European descent, 21% African-American/Hispanic/Asian (Ndis = 135, Nrep = 230)	Prostate cancer	Brachytherapy (TG43 or palladium) ± EBRT (3D or IMRT to 24–50 Gy) or IMRT alone 66.6–81 Gy	Affymetrix v6.0 array, Illumina iSelect custom SNP array	Erectile dysfunction based on SHIM or MSEF questionnaire	12 SNPs near genes involved in ED or cell adhesion and signaling—rs11693002, rs3749191 (*CDCP1*), rs10764930 (*GLRX3*), rs11648233 (*HSD17B2*), rs322895, rs895255, rs148147, rs7245988 (*NLRP11*), rs959567 (*SPATA5*), rs6557362 (*CNKSR3*), rs766838, rs11747037(*KCNN2*), (OR range for all 1.6-5.6)	Yes
Kerns et al. [36], 2013	2-stage GWAS	Patients from the USA, Spain, Netherlands, Canada (Ndis = 764, Nrep = 368)	Low, intermediate, and high-risk prostate cancer	Brachytherapy (^{125}I or ^{103}Pd) ± EBRT, EBRT alone (45 Gy/25 fx or 50–76 Gy with 1.8–2 Gy/fx)	Affymetrix 6.0 array, Illumina iSelect custom SNP array	Self-reported late rectal bleeding (>90 days post-RT)	rs7120482 and rs176306338 (*MTNR1B*|*SLC36A4*, OR = 2.9-3.1), rs10519410 (*PCDH18*; OR = 1.5), rs10255878 (*ACN9*; OR = 5.2)	No
Fachal et al. [38], 2014	3-stage GWAS	Spanish Galician cohort (Ndis = 741), UK (Nrep = 633), North America (Nval = 368)	Intermediate and high-risk prostate cancer	EBRT (conventional 60–74 Gy, IMRT 66.6-81 Gy) alone, Brachy ^{125}I or ^{103}Pd + EBRT 24–50 Gy	Axiom Genome-Wide CEU1 array, Illumina CytoSNP 12 chip, Affymetrix 6.0 array	Acute toxicity (during RT), late toxicity >2 years after RT, and overall toxicity based on STAT scores	rs264663 (*TANC1*; OR = 6.17)	No
Barnett et al. [25], 2014	Discovery GWAS	UK cohort from RAPPER study (Ndis = 633), Spanish cohortfrom Gene-PARE and RAIDIOGEN studie (Nrep = 516, Nval = 862)	Prostate cancer (stage I, II)	EBRT alone, Brachytherapy ^{125}I or ^{103}Pd ± EBRT	Illumina CytoSNP12 array	Toxicity >2 years after RT using STAT scores (incontinence, decreased stream, urine frequency, nocturnal frequency, proctitis, rectal bleeding, fecal incontinence)	rs13116075 (overall toxicity, *CCRN4L*; RR = 1.52), rs12353488 (urinary frequency, no gene; R = 1.52), rs2788612 (rectal incontinence, *KCND3*; RR = 9.91)	No

(Continued to the next page)

https://doi.org/10.3857/roj.2020.00556

https://doi.org/10.3857/roj.2020.00556

Table 1. Continued

Study, year	Study type	Race/ethnic group (sample number)	Cancer type (staging)	RT technique, dose, fractionation	Genotyping technology	Effect and scoring system	Significant polymorphisms (gene; OR/RR)	Model incorporation
Kerns et al. [39], 2016	Meta-analysis	4 cohorts: RAPPER, RADIOGEN, Gene-PARE, CCI from the UK, Spain, USA, Canada, Mainly European	Prostate cancer	EBRT alone, Brachytherapy ^{125}I or ^{103}Pd ± EBRT	Axiom Genome-Wide CEU1 array, Illumina CytoSNP 12 chip, Affymetrix 6.0 array	Rectal bleeding, urinary endpoints (frequency, nocturia), STAT score used for overall late toxicity 1.5–2.5 years post-RT	rs17599026 (urinary frequency, *KDM3B*; OR = 3.12), rs7720298 (decreased urinary stream, *DNAH5*; OR = 2.71)	Yes
Kerns et al. [40], 2020	Meta-analysis	Kerns 2016 cohort including CCI-EBRT and CCI-BT (Ndis = 3,871), Japanese cohort, (Nval = 962)	NCCN risk very low to high or very high-risk prostate cancer	EBRT (3D and IMRT) alone, Brachytherapy ^{125}I or ^{103}Pd ± EBRT, supine position	Axiom Genome-Wide CEU1 array, Illumina CytoSNP 12 chip, Affymetrix 6.0 array	Increased urinary frequency, decreased urinary stream, hematuria, and rectal bleeding (followed 6 months to 5 years post-RT) Overall toxicity using STAT score	rs17055178 (rectal bleeding, no gene; HR = 1.95), rs10969913 (decreased urinary stream, no gene; HR = 3.92), rs11122573 (hematuria, no gene; HR = 1.92), rs147121532 (hematuria, *PGBD5*; HR = 4.42)	Yes
Morton et al. [27], 2017	Discovery GWAS	Majority European descent (N = 2,981)	Childhood survivors of cancer (64% Hodgkin's lymphoma, bone cancer, CNS, retinoblastoma, others)	Chest-directed RT	Illumina Human Omino5Exome array	Secondary breast cancer	rs4342822 (*PROX1*; HR = 1.92), rs74949440 (*TAGLN*; HR = 2.47), rs17020562 (*RPS6KC1*; HR = 41.01)	Yes
Barnett et al. [25], 2014	Discovery GWAS	UK cohorts from RAPPER study (N = 1,217), LeND cohort (Nrep = 516)	Breast cancer	IMRT (median 40 Gy/15 fx over 3 weeks)	Illumina CytoSNP12 array	Toxicity > 2 years after RT using STAT scores (pain, telangiectasia, shrinkage, pigmentation, edema)	rs16958536 (telangiectasia, *SEMA6D*; RR = 1.66), rs2840044 (overall toxicity, *SLFN14*; RR = 1.56), rs12243039 (overall toxicity, *C10orf113*; RR = 3.28)	No
Bourgier et al. [24], 2016	Discovery GWAS	Mostly European descent (N = 150)	Breast cancer (stage I, II)	3D with median 50 Gy/25 fx over 5 weeks ± boost (10–16 Gy at 2 Gy/fx)	Affymetrix 6.0 array	Late radiation-induced lymphocyte apoptosis (RILA)	rs1182531 (*RILA*, *PHACTR3*), rs1182532 (*RILA*, *PHACTR3*)	No
Brooke et al. [31], 2018	Discovery GWAS	> 85% European descent (Ndis = 1,644, Nrep = 1,624)	Childhood cancer survivors (lymphoma, leukemia, CNS tumor, embryonal tumors, others)	Ovarian radiotherapy (range: < 50 Gy and ≥ 2,000 cGy)	Affymetrix HumanSNP6.0 array, Illumina Human Omni5Exome array	Premature menopause	rs9999820 (*NPY2R*; OR = 7.52), rs4402990 (*NPY2R*; OR = 4.19), rs13114936 (*NPY2R*; OR = 5.21), rs4323056 (*NPY2R*; OR6.87)	Yes
Yang et al. [41], 2020	Discovery GWAS	Chinese cohort (N = 1,467)	Nasopharyngeal cancer (stage I-IV)	2D-CRT (68–76 Gy) and IMRT (68–70 Gy/30–33 fx)	Human610-Quad, Infinium Global Screening Array-24	Oral mucositis	rs9484606 (*VTA1*; OR = 1.70), rs16876733 (*PER4*; OR = 1.95), rs117157809 (*TNKS*; OR = 3.72)	No

(Continued to the next page)

Table 1. Continued

Study, year	Study type	Race/ethnic group (sample number)	Cancer type (staging)	RT technique, dose, fractionation	Genotyping technology	Effect and scoring system	Significant polymorphisms (gene; OR/RR)	Model incorporation
Wang et al. [42], 2019	3-stage GWAS	Chinese cohorts (Ndis = 1,082, Nval = 1,119, Nrep = 741)	Nasopharyngeal cancer (stage I-IV)	2D-CRT (68–76 Gy with 2 Gy/fx), IMRT (68–70 Gy for 30–33 fx)	Human610-Quad	Temporal lobe injury, follow-up of 15 years by MRI	rs17111237 (*CEP128*; HR = 1.45), rs16271 (*CEP128*; HR = 1.46)	Yes

RT, radiotherapy; OR, odds ratio; RR, relative risk; Ndis, number of patients used in discovery phase; Nval, number of patients in validation cohort; Nrep, number of patients in replication cohort; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; SHIM, Sexual Health Inventory for Men; EBRT, external beam radiotherapy; 2D-CRT, 2D conformal radiation therapy; STAT, Standardized Total Average Toxicity; MSEF, Mount Sinai Erectile Function; AUASS, American Urological Association Symptom Score; SNP, single nucleotide polymorphism.

sis, lung toxicity and heart cardiotoxicity using data from the CO-HO-RT trial. Because of the rare event-outcome occurrences and modest heart radiation doses of 2.45 Gy and mean lung dose of 5.3 Gy, they were not able to find any significant SNPs related to lung and heart toxicity. However, they were able to identify SNPs located within the *PHACTR3* gene and downstream of *GDF-10* that were associated with late radiation-induced lymphocyte apoptosis and radiation-induced skin fibrosis, respectively (Table 1).

To improve the observance of rare events, a composite score that captured multiple radiation-induced side effects was developed. Barnett et al used the scale-independent Standardized Total Average Toxicity (STAT) score as their primary outcome to identify SNPs associated with toxicity two years after radiotherapy in patients that received adjuvant breast radiotherapy and radical prostate radiotherapy [25]. The STAT score included telangiectasia, breast edema, breast shrinkage, pigmentation, and breast pain. GWAS analysis of individual and STAT scores identified rs2881208, rs882460, rs28400440, and rs13116075 SNPs associated with *SATB2*, *CCDC129*, *SLFN14*, and *CCRN4L* genes, respectively (all risk ratios [RR] > 1.5) (Table 1). Though these associations could not validated at a significance level of 0.05—perhaps because of the limited sample size of the validation cohort—a follow-up study by Mbah et al. [26] supported the role of *SATB2* rs2881208 in predicting late-radiation toxicity, along with age, supine positioning during radiation treatment, and breast volume.

In addition to broadly identifying genetic risk factors, GWAS have also highlighted differences in genetic susceptibility based on radiation dose. GWAS in survivors of childhood cancers that received ≥ 10 Gy of chest irradiation identified SNPs near genes involved in cellular proliferation and migration such as *PROX1* and *TAGLN* (hazard ratio [HR] = 1.92; 95% confidence interval [CI], 1.49–2.44) [27]. Whereas, patients that received < 10 Gy had different SNP risk factors. Interestingly, the SNPs and associated genes identified in this study did not include SNPs and genes such as *BRCA1* and *BRCA2* that increase the risk of primary breast cancer. This discrepancy may be due to the smaller sample size of this study compared to general population GWAS. Alternatively, it is possible that the risk factors for breast cancer in the general population may be different from those that are associated with radiation-induced breast cancer. Some studies have shown no association between genes that increase the risk for developing primary breast cancer compared to breast cancer following chest irradiation [12,27]. Large GWAS are therefore needed to identify radiation-specific genetic susceptibility variants and dose-differences.

Genetic susceptibility to radiation toxicity is not only dose dependent but also dependent on when radiation is administered. Studies of survivors of Hodgkin's lymphoma have shown that the

https://doi.org/10.3857/roj.2020.00556

timing of radiation exposure impacts the risk of developing breast cancer and other long-term side effects [28]. If patients receive chest irradiation during puberty when breast development is occurring, they have a higher risk for breast cancer than those patients that receive irradiation post-breast development. Similarly, polymorphisms near the *ATG5* and *PRDM1* genes were predictors for secondary malignancies for patients irradiated during childhood, but not for those irradiated as adults [29]. Timing of radiotherapy also suggests a role for the circadian rhythm in the development of radiation-induced late side effects. Though identified through a candidate gene approach, circadian rhythm variants, *PER3* and *NOCT A*, were predictive of worse acute and late toxicity if radiotherapy was administered in the morning compared to the afternoon in patients with breast cancer [30]. Normal tissue toxicity is likely fluctuating during a person's lifetime and may be influenced by baseline health status, such that patients with comorbidities may be at higher risk for developing radiation-induced adverse side effects compared to their healthier counterparts.

Pelvic Irradiation

Radiation and tissue specific genetic susceptibility are also observed in radiation-induced genitourinary toxicity. Female childhood cancer survivors that received pelvic irradiation develop therapy-related premature menopause (PM) at a 10-fold rate higher than their sibling controls. Therefore, efforts have focused on identifying patients that would benefit most from cryopreservation of oocytes prior to starting radiotherapy. Using a two-stage GWAS approach, whereby top-ranked SNPs identified in the first cohort are genotyped in a second cohort, Brooke et al. [31] prospectively followed 799 female survivors of childhood cancer for the development of PM. Adjusting for cyclophosphamide equivalent doses of alkylating agents and ovarian radiation doses they identified 13 SNPs on Chromosome 4 that increased the risk for PM with an odds ratio (OR) of 25.89 in the discovery phase, and an OR of 3.97 in the replication phase. This haplotype was prevalent in 50% of those with PM, and only observed in 3.8% of controls and in 1.4% of the general female population. SNPs were found near the *NPY2R* gene, which is known to regulate gonadotropin-releasing hormones pulses, luteinizing hormone levels and ovulation [32]. Variations in expression of genes controlling hormone expression may therefore increase the risk for gonadotoxicity and subsequently lead to premature menopause.

Pelvic irradiation to the prostate in the form of localized brachytherapy, with or without external beam radiation therapy (EBRT), is also associated with radiation-induced side effects in 5%–10% of patients. Side effects can include erectile dysfunction (ED), rectal bleeding, urinary and fecal incontinence, decreased urinary stream, and proctitis. The first GWAS looking at radiation-induced side effects in prostate cancer studied ED risk [33]. GWAS identified SNPs located near genes involved in cell adhesion and cell matrix association, rather than radiation-affected pathways, such as DNA damage repair [34]. There were also group enriched SNPs near the *FSHR* gene that increased the risk for radiation-induced ED in African Americans [33]. This study and others revealed that increasing the number of alleles increases the risk of erectile dysfunction [33,34]. Younger men with more risk alleles had a similar likelihood of developing ED as older men with fewer risk alleles. One allele had an OR of 2.2, while multiple alleles had an OR >2.2 [34]. Furthermore, incorporation of SNPs into a multivariate model along with ancestry was more accurate in predicting ED than clinical factors alone such as stage, Gleason score, and pre-treatment sexual function (area under the curve [AUC] for genetic model = 0.983 vs. AUC for clinical model = 0.749) [33]. Though not directly addressed in this study, incorporation of both genetic risk factors and clinical metrics can increase the predictability of these models.

GWAS have also been used to identify polymorphisms associated with changes in late-toxicity such as changes urinary function, rectal bleeding, and overall toxicity. Eight SNPs, including one associated with *MYO3B* (rs13035033), increased the risk for urinary straining [35]; though this finding could not be replicated [37]. GWAS of individual endpoints such as rectal bleeding identified SNPs near genes regulating vascular proliferation [36], while markers of overall toxicity identified *TANC1*, a gene involved in muscle regeneration, as a risk factor [38]. To increase the power to detect rare polymorphisms, Kerns et al. [39] used a meta-analysis approach to identify SNPs associated with increased urinary frequency, rectal bleeding, decreased stream and overall toxicity. This study validated previous SNPs, discovered new SNPs, and most notably it showed that multiple data sets could be combined to increase the power of GWAS. A follow-up meta-analysis study included additional samples from a Japanese cohort to identify new polymorphisms associated with hematuria, and validated SNPs previously associated with increased urinary frequency, decreased urinary stream, and overall toxicity [40]; again emphasizing the power of analyzing GWAS datasets in aggregate.

Head and Neck Irradiation

Oral mucositis is an acute complication of head and neck irradiation. To identify patients that would be at risk for adverse oral mucositis outcomes, Yang et al. [41] performed a GWAS in more than 1,000 nasopharyngeal carcinoma patients receiving radiotherapy. Using gene set analyses of their identified variants they were able

to link telomere biological processes to radiotherapy toxicity and thereby illustrate the use of GWAS in enhancing our understanding of radiobiology.

Temporal lobe injury is a late radiation-induced side effect in patients with nasopharyngeal carcinoma. Genetic susceptibility studies for radiation-induced central nervous system toxicity are starting to emerge. Wang et al. [42] conducted a three-stage GWAS study with more than 1,000 patients for each stage. Their analysis identified SNPs near the gene *CEP128*, which codes a centrosome protein involved in cell cycle progression, and is associated with temporal lobe injury risk (HR = 1.45; 95% CI, 1.26–1.66). Furthermore, they discovered that 12.7% of the GWAS-based genes were associated with the neurogenesis pathway. SNP (missing period) differences associated with the *CEP128* gene were also associated with changes in levels of expression [43]. These results suggest again that radiation-induced injury is likely affecting tissue specific cellular pathways.

Models of Radiation Toxicity

GWAS have provided novel insight into radiobiological processes not otherwise recognized through candidate-gene approaches. They have also highlighted the differences in genetic susceptibility due to radiation dosing and timing of administering radiation. GWAS have distinguished polymorphisms comparing tissue-specific toxicity versus overall toxicity and acute versus late radiotherapy side effects. Two proposed models may in part explain the complexity of genetic susceptibility to radiation—a deterministic model and a stochastic model [10,44]. Under a deterministic model, each tissue can have its own threshold for toxicity and these thresholds can vary between patients. In a stochastic model, radiation may impact cellular function through general processes such as increasing reactive-oxygen species and promoting genomic instability. These processes would nonspecifically affect pathways that increase the risk of radiation-induced side effects. Variability in observing deterministic or stochastic processes would depend on individual patient genetic vulnerability. Patients with polymorphisms that increase stochastic events may be at higher risk for overall toxicity, whereas patients with polymorphisms affecting tissue-specific pathways would manifest more restricted side effects. Phenotypic expression of adverse effects would thus be dependent on genetic susceptibility and life style factors. For example, if the patient is already at risk for developing erectile dysfunction, both genetically and because of lifestyle factors, exposure to radiation may be the last "hit" required for the development of ED through a deterministic or stochastic process. GWAS and candidate-gene approaches have been successful in identifying "general" toxicity polymorphisms and side-effect specific polymorphisms. Integration of cellular assays, "omic" data such as transcriptome-wide association studies (TWAS) and proteomics will aid in distinguishing between the two processes at the patient level.

GWAS Challenges and Opportunities

Despite recent progress and its promise to personalize patient care, integration of GWAS findings into clinical settings remains a challenge. Reproducibility is often hard to achieve because of small sample sizes, which decrease the statistical power needed to detect moderate-to-weakly associated polymorphisms, and high false positives from multiple-hypothesis testing. To address these challenges, the Radiogenomics Consortium encouraged standardization of reporting of GWAS, central pooling of large databases, and standardization in reporting acute and late side effects [14]. Combining multiple datasets, however, posed additional statistical challenges that have now spawned new mathematical models and statistical approaches. These mathematical models have been applied with success to predict radiotherapy complications such as late rectal bleeding and erectile dysfunction and have identified biological processes of radiation damage [45,46].

Incorporation of GWAS findings into machine learning also has the potential to increase the clinical utility of GWAS. Lee et al. [47] used machine learning-based multivariate modeling to predict four urinary symptoms following radiation therapy. They found that weak stream was predicted when the top 75% of SNPs were included in their model compared to a model that only included clinical predictors (R^2 of 0.80 vs. R^2 of 0.60). Machine learning algorithms can be applied to integrate genetic data, clinical correlates, and patient characteristics to build models that can evolve as patients' characteristics change through the course of treatment [48]. However, in order for models to be truly predictive, racially heterogeneous populations must be included.

It is known that polymorphisms can vary by race/ethnic groups. For example, SNPs associated with the *TGFb1* promoter and the *NFE2L2* promoters were associated with late radiation effects in African Americans, but not Whites [49]. The failure to include diverse patient groups in GWAS has two main effects: (1) decreased discovery potential and generalizability and (2) decreased predictive power of model building. Although there is concern that inclusion of non-European populations increases the signal-to-noise ratio, low frequency variants or variants that are completely absent in European populations may be missed [50]. In addition, the effect sizes of identified variants in one group may be the different in other populations. Wojcik et al. [51] used a large data set that included Hispanic populations, African-American, Asian, Native Ha-

 https://doi.org/10.3857/roj.2020.00556

waiian, Native American, and multi-ethnic individuals to show that the effect size of published trait-variant associations were significantly weaker in Hispanic and African-American populations. Predictive models based on these effect sizes and variants could potentially result in erroneous predictions that could further increase already existing health disparities. Thus, recruitment of under-represented groups, development of algorithms robust to the inclusion of heterogeneous populations, building of databases, and integration with other "omic" data, will strengthen the clinical potential of GWAS.

Conclusion

Since its adoption in radiation oncology, GWAS have identified polymorphisms that increase genetic susceptibility to radiation-induced tissue toxicity. However, challenges in high false rate discoveries due to multiple hypothesis testing and small sample sizes have failed to reproduce some results. Development of techniques to score side effects and standardize GWAS reporting, along with the establishment of the Radiogenomics Consortium have partly overcome some of the challenges inherent in GWAS. Meta-analyses of GWAS now include larger patient cohorts, more diverse populations, multiple steps of validation, and new statistical approaches. Incorporation of genetic susceptibility of normal tissue, tumor radiosensitivity, clinical markers, and patient characteristics into adaptive models is poised to make genomically-guided radiotherapy a reality.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012;9:193-9.
2. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-induced lung injury: assessment and management. Chest 2019;156:150-62.
3. Soumarova R, Rusinova L. Cardiotoxicity of breast cancer radiotherapy: overview of current results. Rep Pract Oncol Radiother 2020;25:182-6.
4. Kelsey CR, Broadwater G, James O, et al. Phase 2 study of dose-reduced consolidation radiation therapy in diffuse large B-cell lymphoma. Int J Radiat Oncol Biol Phys 2019;105:96-101.
5. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385-95.
6. Scaife JE, Barnett GC, Noble DJ, et al. Exploiting biological and physical determinants of radiotherapy toxicity to individualize treatment. Br J Radiol 2015;88:20150172.
7. Rosenstein BS. Radiogenomics: identification of genomic predictors for radiation toxicity. Semin Radiat Oncol 2017;27:300-9.
8. Barnett GC, West CM, Dunning AM, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009;9:134-42.
9. Thomas RJ, Holm M, Williams M, et al. Lifestyle factors correlate with the risk of late pelvic symptoms after prostatic radiotherapy. Clin Oncol (R Coll Radiol) 2013;25:246-51.
10. Habash M, Bohorquez LC, Kyriakou E, Kron T, Martin OA, Blyth BJ. Clinical and functional assays of radiosensitivity and radiation-induced second cancer. Cancers (Basel) 2017;9:147.
11. Ahmed M, Dorling L, Kerns S, et al. Common genetic variation associated with increased susceptibility to prostate cancer does not increase risk of radiotherapy toxicity. Br J Cancer 2016;114:1165-74.
12. Dorling L, Barnett GC, Michailidou K, et al. Patients with a high polygenic risk of breast cancer do not have an increased risk of radiotherapy toxicity. Clin Cancer Res 2016;22:1413-20.
13. Rattay T, Talbot CJ. Finding the genetic determinants of adverse reactions to radiotherapy. Clin Oncol (R Coll Radiol) 2014;26:301-8.
14. West C, Rosenstein BS, Alsner J, et al. Establishment of a Radiogenomics Consortium. Int J Radiat Oncol Biol Phys 2010;76:1295-6.
15. Kerns SL, de Ruysscher D, Andreassen CN, et al. STROGAR: STrengthening the Reporting Of Genetic Association studies in Radiogenomics. Radiother Oncol 2014;110:182-8.
16. Chargari C, Riet F, Mazevet M, Morel E, Lepechoux C, Deutsch E. Complications of thoracic radiotherapy. Presse Med 2013;42(9 Pt 2):e342-51.
17. Cheng YJ, Nie XY, Ji CC, et al. Long-term cardiovascular risk after radiotherapy in women with breast cancer. J Am Heart Assoc 2017;6:e005633.
18. Chang-Claude J, Popanda O, Tan XL, et al. Association between polymorphisms in the DNA repair genes, XRCC1, APE1, and XPD and acute side effects of radiotherapy in breast cancer patients. Clin Cancer Res 2005;11:4802-9.
19. Chang-Claude J, Ambrosone CB, Lilla C, et al. Genetic polymorphisms in DNA repair and damage response genes and late normal tissue complications of radiotherapy for breast cancer. Br J

Cancer 2009;100:1680-6.
20. Yin M, Liao Z, Liu Z, et al. Functional polymorphisms of base excision repair genes XRCC1 and APEX1 predict risk of radiation pneumonitis in patients with non-small cell lung cancer treated with definitive radiation therapy. Int J Radiat Oncol Biol Phys 2011;81:e67-73.
21. Andreassen CN, Rosenstein BS, Kerns SL, et al. Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. Radiother Oncol 2016;121:431-9.
22. Du L, Yu W, Dai X, et al. Association of DNA repair gene polymorphisms with the risk of radiation pneumonitis in lung cancer patients. Oncotarget 2017;9:958-68.
23. Delgado BD, Enguix-Riego MV, Fernandez de Bobadilla JC, et al. Association of single nucleotide polymorphisms at HSPB1 rs7459185 and TGFB1 rs11466353 with radiation esophagitis in lung cancer. Radiother Oncol 2019;135:161-9.
24. Bourgier C, Kerns S, Gourgou S, et al. Concurrent or sequential letrozole with adjuvant breast radiotherapy: final results of the CO-HO-RT phase II randomized trial. Ann Oncol 2016;27:474-80.
25. Barnett GC, Thompson D, Fachal L, et al. A genome wide association study (GWAS) providing evidence of an association between common genetic variants and late radiotherapy toxicity. Radiother Oncol 2014;111:178-85.
26. Mbah C, de Ruyck K, de Schrijver S, et al. A new approach for modeling patient overall radiosensitivity and predicting multiple toxicity endpoints for breast cancer patients. Acta Oncol 2018;57:604-12.
27. Morton LM, Sampson JN, Armstrong GT, et al. Genome-wide association study to identify susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer. J Natl Cancer Inst 2017;109:djx058.
28. Hodgson DC, Koh ES, Tran TH, et al. Individualized estimates of second cancer risks after contemporary radiation therapy for Hodgkin lymphoma. Cancer 2007;110:2576-86.
29. Best T, Li D, Skol AD, et al. Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma. Nat Med 2011;17:941-3.
30. Johnson K, Chang-Claude J, Critchley AM, et al. Genetic variants predict optimal timing of radiotherapy to reduce side-effects in breast cancer patients. Clin Oncol (R Coll Radiol) 2019;31:9-16.
31. Brooke RJ, Im C, Wilson CL, et al. A high-risk haplotype for premature menopause in childhood cancer survivors exposed to gonadotoxic therapy. J Natl Cancer Inst 2018;110:895-904.
32. Xu M, Hill JW, Levine JE. Attenuation of luteinizing hormone surges in neuropeptide Y knockout mice. Neuroendocrinology 2000;72:263-71.
33. Kerns SL, Ostrer H, Stock R, et al. Genome-wide association study to identify single nucleotide polymorphisms (SNPs) associated with the development of erectile dysfunction in African-American men after radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;78:1292-300.
34. Kerns SL, Stock R, Stone N, et al. A 2-stage genome-wide association study to identify single nucleotide polymorphisms associated with development of erectile dysfunction following radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85:e21-8.
35. Kerns SL, Stone NN, Stock RG, Rath L, Ostrer H, Rosenstein BS. A 2-stage genome-wide association study to identify single nucleotide polymorphisms associated with development of urinary symptoms after radiotherapy for prostate cancer. J Urol 2013;190:102-8.
36. Kerns SL, Stock RG, Stone NN, et al. Genome-wide association study identifies a region on chromosome 11q14.3 associated with late rectal bleeding following radiation therapy for prostate cancer. Radiother Oncol 2013;107:372-6.
37. Schack LM, Petersen SE, Nielsen S, et al. Validation of genetic predictors of late radiation-induced morbidity in prostate cancer patients. Acta Oncol 2017;56:1514-21.
38. Fachal L, Gomez-Caamano A, Barnett GC, et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. Nat Genet 2014;46:891-4.
39. Kerns SL, Dorling L, Fachal L, et al. Meta-analysis of genome wide association studies identifies genetic markers of late toxicity following radiotherapy for prostate cancer. EBioMedicine 2016;10:150-63.
40. Kerns SL, Fachal L, Dorling L, et al. Radiogenomics Consortium Genome-Wide Association study meta-analysis of late toxicity after prostate cancer radiotherapy. J Natl Cancer Inst 2020;112:179-90.
41. Yang DW, Wang TM, Zhang JB, et al. Genome-wide association study identifies genetic susceptibility loci and pathways of radiation-induced acute oral mucositis. J Transl Med 2020;18:224.
42. Wang TM, Shen GP, Chen MY, et al. Genome-wide association study of susceptibility loci for radiation-induced brain injury. J Natl Cancer Inst 2019;111:620-8.
43. Dean B, Parkin GM, Gibbons AS. Associations between catechol-O-methyltransferase (COMT) genotypes at rs4818 and rs4680 and gene expression in human dorsolateral prefrontal cortex. Exp Brain Res 2020;238:477-86.
44. Herskind C, Talbot CJ, Kerns SL, Veldwijk MR, Rosenstein BS, West CM. Radiogenomics: a systems biology approach to understanding genetic risk factors for radiotherapy toxicity? Cancer Lett

2016;382:95-109.
45. Oh JH, Kerns S, Ostrer H, Powell SN, Rosenstein B, Deasy JO. Computational methods using genome-wide association studies to predict radiotherapy complications and to identify correlative molecular processes. Sci Rep 2017;7:43381.
46. Kang J, Coates JT, Strawderman RL, Rosenstein BS, Kerns SL. Genomics models in radiotherapy: from mechanistic to machine learning. Med Phys 2020;47:e203-17.
47. Lee S, Kerns S, Ostrer H, Rosenstein B, Deasy JO, Oh JH. Machine learning on a genome-wide association study to predict late genitourinary toxicity after prostate radiation therapy. Int J Radiat Oncol Biol Phys 2018;101:128-35.
48. El Naqa I, Kerns SL, Coates J, et al. Radiogenomics and radiotherapy response modeling. Phys Med Biol 2017;62:R179-206.
49. Alam A, Mukhopadhyay ND, Ning Y, et al. A preliminary study on racial differences in HMOX1, NFE2L2, and TGFβ1 gene polymorphisms and radiation-induced late normal tissue toxicity. Int J Radiat Oncol Biol Phys 2015;93:436-43.
50. Bentley AR, Callier S, Rotimi CN. Diversity and inclusion in genomic research: why the uneven progress? J Community Genet 2017;8:255-66.
51. Wojcik GL, Graff M, Nishimura KK, et al. Genetic analyses of diverse populations improves discovery for complex traits. Nature 2019;570:514-8.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):236-243
https://doi.org/10.3857/roj.2020.00738

Post-mastectomy radiation therapy in breast reconstruction: a patterns of care study of the Korean Radiation Oncology Group

Gowoon Yang[1], Jee Suk Chang[1], Kyung Hwan Shin[2], Jin Ho Kim[2], Won Park[3], Haeyoung Kim[3], Kyubo Kim[4], Ik Jae Lee[5], Won Sup Yoon[6], Jihye Cha[7], Kyu-Chan Lee[8], Jin Hee Kim[9], Jin Hwa Choi[10], Sung-Ja Ahn[11], Boram Ha[12], Sun Young Lee[13], Dong Soo Lee[14], Jeongshim Lee[15], Sei One Shin[16], Yong Bae Kim[1]

[1]*Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea*
[2]*Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea*
[3]*Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[4]*Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, Korea*
[5]*Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea*
[6]*Department of Radiation Oncology, Korea University Ansan Hospital, Korea University College of Medicine, Seoul, Korea*
[7]*Department of Radiation Oncology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, Korea*
[8]*Department of Radiation Oncology, Gachon University Gil Medical Center, Incheon, Korea*
[9]*Department of Radiation Oncology, Keimyung University Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea*
[10]*Department of Radiation Oncology, Chung-Ang University Hospital, Seoul, Korea*
[11]*Department of Radiation Oncology, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea*
[12]*Department of Radiation Oncology, Hallym University Dongtan Sacred Heart Hospital, Hwasung, Korea*
[13]*Department of Radiation Oncology, Chonbuk National University Hospital, Jeonju, Korea*
[14]*Department of Radiation Oncology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Korea*
[15]*Department of Radiation Oncology, Inha University Hospital, Inha University School of Medicine, Incheon, Korea*
[16]*Department of Radiation Oncology, Andong Medical Group Andong Hospital, Andong, Korea*

Received: September 27, 2020
Revised: November 15, 2020
Accepted: November 25, 2020

Correspondence:
Jee Suk Chang
Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-8117
Fax: +82-2-2227-7823
E-mail: changjeesuk@yuhs.ac
ORCID:
https://orcid.org/0000-0001-7685-3382

Purpose: The details of breast reconstruction and radiation therapy (RT) vary between institutions; therefore, we sought to investigate the practice patterns of radiation oncologists who specialize in breast cancer.

Materials and Methods: We identified the practice patterns and inter-hospital variations from a multi-center cohort of women with breast cancer who underwent post-mastectomy RT (PMRT) to the reconstructed breast at 16 institutions between 2015 and 2016. The institutions were requested to contour the target volume and produce RT plans for one representative case with five different clinical scenarios and answer questionnaires which elicited infrastructural information. We assessed the inter-institutional variations in RT in terms of the target, normal organ delineation, and dose-volume histograms.

Results: Three hundred fourteen patients were included; 99% of them underwent immediate reconstruction. The most irradiated material was tissue expander (36.9%) followed by transverse rectus abdominis musculocutaneous flap (23.9%) and silicone implant (12.1%). In prosthetic-based reconstruction with tissue expander, most patients received PMRT following partial deflation. Conventional fractionation and hypofractionation RT were used in 66.6% and 33.4% patients, respectively (commonest: 40.05 Gy in 15 fractions [17.5%]). Furthermore, 15.6% of the patients received boost RT and 53.5% were treated with bolus. Overall, 15 physicians responded to the questionnaires and six submitted their contours and RT plans. There was a significant variability in target delineations and RT plans between physicians, and between clinical scenarios.

Conclusion: Adjuvant RT following post-mastectomy reconstruction has become a common practice in Korea. The details vary significantly between institutions, which highlights an urgent need for standard protocol in this clinical setting.

Keywords: Radiotherapy, Mammaplasty, Breast neoplasm

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Breast reconstruction has become very common over the last two decades [1,2]. It significantly improves the quality of life and reduces adverse psychosocial effects following mastectomy [3]. However, the decision regarding breast reconstruction becomes complicated in patients who anticipate to receive post-mastectomy radiation therapy (PMRT) [4]. The majority of radiation oncologists believe that their ability to deliver radiotherapy to the chest wall is challenged by immediate breast reconstruction [5]. Simultaneously, the majority of reconstructive surgeons believe that the cosmetic outcomes of breast reconstruction are negatively affected by PMRT [6,7].

Reconstructions can either be immediate or delayed or a combined approach called delayed-immediate reconstruction [8]. An implant, autologous tissue or a combination of an implant and a flap, can be used for the restoration of the breast mound [9]. All reconstruction approaches have their own pros and cons [10,11]. The techniques available for radiotherapy delivery in patients with breast cancer who have undergone reconstruction have improved over the past decade, which has reduced the challenges in radiotherapy planning that once seemed difficult to overcome. Despite the improvements in both reconstruction and radiotherapy techniques, several issues still require to be answered, such as the type of reconstruction that is the most feasible with PMRT, the timing of reconstruction relative to PMRT, and optimization of radiotherapy to minimize treatment-related complications without compromising the oncological and cosmetic outcomes.

The practice patterns may vary between institutions regarding the reconstruction type and radiotherapy planning and delivery. However, there are no standard protocols or guidelines in clinical settings. Therefore, the aim of this study was to investigate the practice patterns of PMRT in breast reconstruction in Korea.

Materials and Methods

1. Ethical statement

After approval from the review board of the Korean Radiation Oncology Group (KROG 18-04) and Severance Hospital Institutional Review Board (No. 4-2017-0931), a retrospective multi-center observational study and a dummy run study were conducted in patients with breast cancer who received RT and underwent breast reconstruction to identify the practice patterns.

2. Observational study

The inclusion criteria were as the following: histologically proven breast cancer, non-metastatic disease, female sex, and breast reconstruction following mastectomy and subsequent adjuvant RT between 2015 and 2016. The reconstruction rate has increased since 2015 after reimbursement by the Korean National Insurance Service and we surmised that it was actively performed during this period. Patients who underwent bilateral mastectomy for bilateral breast cancer or were male sex, or lost to follow-up were excluded. The medical charts of the patients were collected and retrospectively reviewed after approval from each participating center.

The following parameters were analyzed: age, body mass index, smoking history, history of diabetes, clinical T and N stages, multicentricity, systemic therapy, mastectomy (standard, skin-sparing, and nipple-sparing), resection margin (clear, close, and positive), reconstruction sequence (one-stage vs. two-stage), reconstruction timing (immediate vs. delayed), reconstruction options (autologous-based vs. prosthetic-based), reconstruction material at the time of RT (tissue expander, implant, transverse rectus abdominis musculocutaneous flap, deep inferior epigastric perforator flap, latissimus dorsi flap, and others), bilateral reconstruction, operation time, RT technique (three-dimensional conformal, field-in-field, step-and-shot intensity-modulated radiotherapy, and volumetric arc therapy), RT dose/fraction, estimated maximum dose in chest wall on RT planning system, chest wall boost RT, bolus material used, and use of regional RT (Table 1).

3. Dummy run study

The institutions participating in the Division of Breast Cancer, KROG were invited to participate in the present dummy run. They were requested to answer questionnaires (Supplementary A) regarding the infrastructural information, which included computed tomography (CT) simulation, radiation treatment planning (RTP) system, RT treatment details, and quality assurance (QA) activity for the RT machine. CT images from one anonymized patient was provided as a representative case with five different clinical scenarios (cases 1–5) (Supplementary Fig. S1). The physicians from the participating institutions downloaded these CT images from a website and registered them in their own RTP systems; subsequently, they designed RT treatment plans for each clinical scenario. The target range, dose prescription, treatment technique, and beam information were obtained through the questionnaire. RT files in the Digital Imaging and Communications in Medicine (DICOM) format for the structure sets and radiation doses were submitted along with the questionnaires.

4. Data analysis

All analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp., Armonk, NY, USA) using two-sided statistical tests. Descriptive analyses were performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

Table 1. Baseline characteristics (n = 314)

Characteristic	Value
Age (yr)	43.5 ± 8.3
< 40	116 (36.9)
≥ 40	198 (63.1)
BMI (kg/m^2)	22.6 ± 3.3
Smoking	
Current	4 (1.3)
Ever	4 (1.3)
No	299 (95.2)
Unknown	7 (2.2)
Diabetes mellitus	
No	300 (95.5)
Yes	14 (4.5)
Clinical T stage	
T1	70 (22.3)
T2	152 (48.4)
T3	61 (19.4)
T4	27 (8.6)
Unknown	4 (1.3)
Clinical N stage	
N0	51 (16.2)
N+	260 (82.8)
Unknown	3 (0.6)
Multicentricity	
No	187 (59.6)
Yes	126 (40.1)
Unknown	1 (0.3)
Systemic Tx	
Neoadjuvant chemo	165 (52.5)
Adjuvant chemo	187 (59.6)
Endocrine Tx	230 (73.2)
Anti-HER2 Tx	125 (39.8)
Mastectomy	
Standard total	163 (51.9)
Skin sparing	74 (23.6)
Nipple sparing	77 (24.5)
Resection margin	
Complete	276 (87.9)
Close	23 (7.3)
Positive	12 (3.8)
Unknown	3 (1.0)

Values are presented as median ± standard deviation or number (%).
BMI, body mass index; Tx, treatment; HER2, human epidermal growth factor receptor 2.

Table 2. Reconstruction treatments (n = 314)

Variable	Value
Reconstruction stage	
One-stage	160 (51.0)
Two-stage	154 (49.0)
Reconstruction timing	
Immediate	312 (99.4)
Delayed	2 (0.6)
Reconstruction type	
Prosthetic-based	190 (60.5)
ADM use	171 (54.5)
Autologous-based	122 (23.0)
Both	2 (0.6)
Reconstruction status at the time of RT	
Tissue expander	116 (36.9)
TRAM	75 (23.9)
Silicone implant	39 (12.0)
DIEP	29 (9.2)
LD	12 (3.8)
Others	43 (14.0)
Bilateral reconstruction, yes	34 (10.8)
Operation time (hr)	4.8 ± 3.1

Values are presented as number (%) or median ± standard deviation.
ADM, acellular dermal matrix; RT, radiotherapy; TRAM, transverse rectus abdominis myocutaneous; DIEP, deep inferior epigastric perforator; LD, latissimus dorsi.

Results

1. Observational study

Overall, 314 patients treated with PMRT for reconstructed breasts between 2015 and 2016 at the 16 institutions were included. During the same study period, approximately 1,105 patients were referred for PMRT. Table 2 and Fig. 1 present the details of the reconstruction treatments. Most of the patients (99%) underwent immediate reconstruction. One-stage or autologous reconstruction was more frequent than two-stage or prosthetic reconstruction when PMRT was administered. A variety of materials were used for the reconstruction. The most commonly used material was tissue expander (36.9%) followed by TRAM flap (23.9%), silicone implant (12.1%), and a combination of tissue expander and silicone implant (11.2%). When tissue expander was used in prosthetic-based reconstruction, most patients (39.2%) received PMRT after partial deflation. Table 3 presents the details of radiotherapy. Conventional fractionation RT was used in 66.6% of the patients, while hypofractionation was used in 33.4% of patients (commonest: 40.05 Gy in 15 fractions [17.5%]). Additionally, 15.6% of the patients received boost RT and 53.5% of the patients were treated with a bolus.

2. Dummy run and questionnaire

Overall, 15 physicians responded to the questionnaires and six physicians submitted their contours and RT plans (Fig. 1). According to the questionnaires, the prescribed dosage varied between physicians'. Generally, conventional fractionation with 50–50.4 Gy and

https://doi.org/10.3857/roj.2020.00738

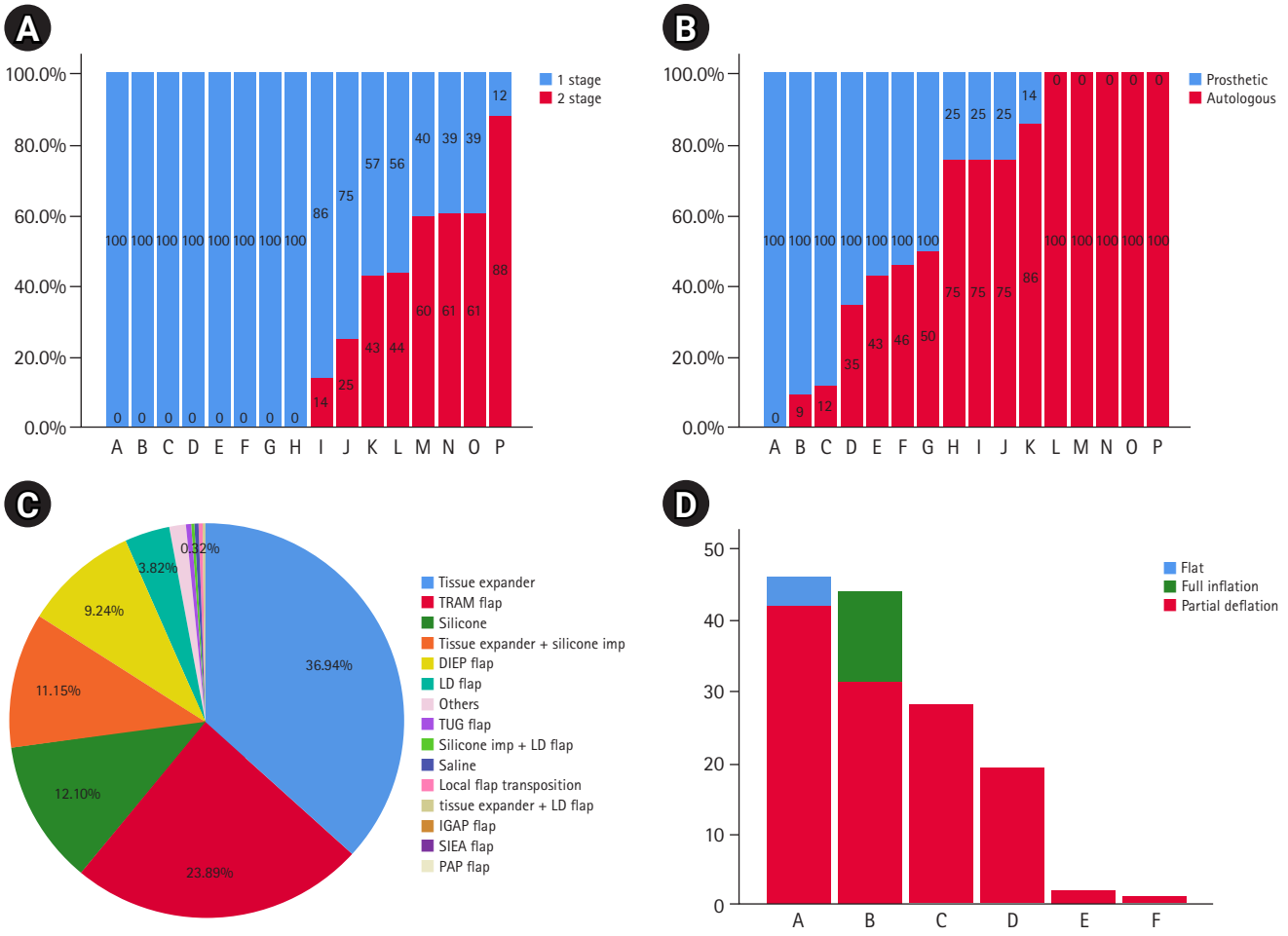


Fig. 1. Reconstruction details. (A) One-stage vs. two-stage reconstruction. (B) Prosthetic vs. autologous reconstruction. (C) Materials used for reconstruction. (D) Inflation status of the tissue expander at the time of radiation therapy. TRAM, transverse rectus abdominis myocutaneous; DIEP, deep inferior epigastric perforator; LD, latissimus dorsi; TUG, transverse upper gracilis; IGAP, inferior gluteal artery perforator; SIEA, superficial inferior epigastric artery; PAP, profunda artery perforator.

over 25–28 fractions was the commonest practice. In a case where a patient was diagnosed with initial clinical internal mammary node metastasis (case 3), one physician responded with prescription of boost dose of 10 Gy in 5 fractions to the internal mammary node after 50 Gy in 25 fractions. Another physician responded with a total dose of 52.8 Gy in 16 fractions with simultaneous integrated boost technique to the internal mammary node. In a case where a patient presented with positive surgical resection margin (case 5), one physician responded with prescription of 54 Gy (Fig. 2). In the questionnaire-based study, 62.5% of physicians replied that they would prescribe boost dose. The most common boost doses that were prescribed included 10 Gy in 5 fractions and 14.4 Gy in 8 fractions. Furthermore, 58.7% of physicians responded that they preferred to not use bolus in their treatments. However, 90% responded that they would use bolus for the patient with positive surgical resection margins (case 5) (Fig. 3).

In terms of target volume delineation, the structures included in the target volume varied significantly between physicians, even within the same clinical scenario (Figs. 4 and 5; Supplementary Fig. S1). In a case where the patient was diagnosed with initial clinical internal mammary node metastasis (case 3), 13/15 physicians included the internal mammary node in the target volume. In a case of the patient who underwent pre-pectoral reconstruction instead of subpectoral reconstruction (case 4), 11/15 physicians included the tissue expander in the target volume. The dose-volume histograms were also analyzed. As for the planning target volume (PTV), it varied widely between physicians' plans, even within the same clinical scenario. The median PTV volume was 563.67 mL (range, 278.84 to 1,100.77 mL; standard deviation [SD], 209.05 mL). Similarly, there was a wide difference in the mean lung dose; the median mean lung dose was 13.26 Gy (range, 5.33 to 18.80 Gy; SD, 4.60 Gy). There was also a wide variance in terms of lung V5 and V20; their median values were 43.89 mL (range, 16.35 to 99.45 mL; SD, 26.64 mL), 23.65 mL (range, 6.7 to 34.03 mL; SD, 10.30 mL), respectively (Table 4).

Table 3. Radiation treatments (n = 314)

Variable	Value
Simulation position	
Supine	305 (97.1)
Prone	2 (0.6)
Unknown	7 (2.2)
RT technique	
Forward IMRT (field-in-field)	124 (39.5)
Arc-IMRT	90 (28.7)
Tangent, 3D	58 (18.5)
Static-IMRT	26 (8.3)
Helical tomo	8 (2.5)
2D (tangential)	1 (0.3)
Unknown	7 (2.2)
Fractionation	
Conventional	209 (66.6)
Hypofractionation	105 (33.4)
Use of boost RT, yes	49 (15.6)
Boost RT dose (Gy)	9 ± 3.8
Expander status	
Full deflation	4 (1.3)
Partial deflation	123 (39.2)
Full inflation	13 (4.1)
Use of bolus	
No	146 (46.5)
Yes	168 (53.5)
Bolus off timing (Gy)	34.2 ± 14.6
Use of regional RT	
No	18 (5.7)
AXL	7 (2.2)
SCL	52 (16.6)
IMN	1 (0.3)
AXL + SCL	74 (23.6)
AXL + IMN	1 (0.3)
SCL + IMN	4 (1.3)
AXL + SCL + IMN	157 (50.0)

Values are presented as number (%) or median ± standard deviation.
IMRT, intensity-modulated radiotherapy; RT, radiotherapy; AXL, axillary lymph node; SCL, supraclavicular lymph node; IMN, internal mammary node.

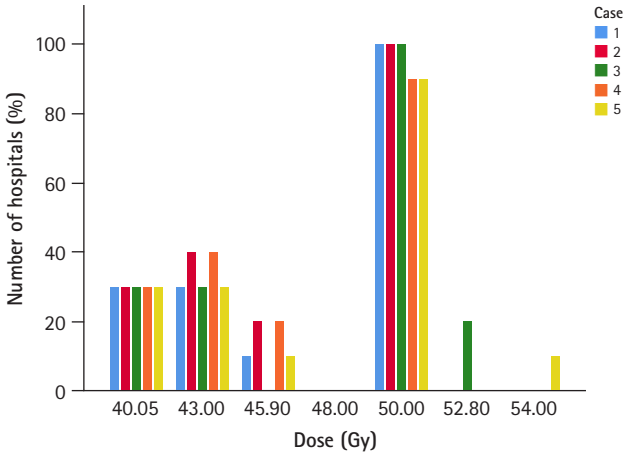


Fig. 2. Dose prescriptions according to different clinical scenarios.

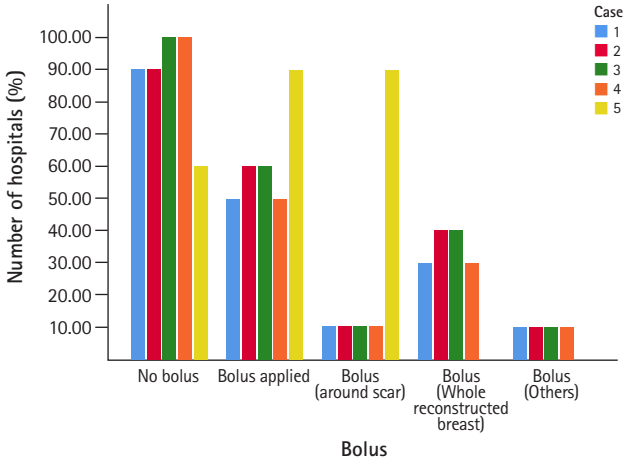


Fig. 3. Details of bolus application.

Discussion and Conclusion

According to the Korean Breast Cancer Society (KBCS) registry, the number of breast reconstruction surgeries has increased almost 3-fold between 2002 and 2013 [12]. In the 2017 KBCS report, the rate of reconstruction after mastectomy was 39.1%, 33.7%, and 9.4% in those in the age-group of < 40, 40–59, and ≥ 60 years, respectively [13]. In the present study, approximately one-third of patients who underwent PMRT underwent breast reconstruction and this rate is expected to increase in the future. The primary goal in the treatment of women with breast cancer who undergo reconstruction and PMRT is to minimize the complications without compromising the oncological outcomes. Therefore, understanding the practice patterns is crucial for the communication between the patients and surgeons. To our knowledge, this is the first study to report the practice patterns of PMRT in the setting of breast reconstruction in Korea.

Both RT techniques and breast reconstruction techniques have evolved over time. In the present study, a majority of the patients underwent immediate reconstruction; the rate of one-stage, two-stage, autologous-based, and prosthetic-based reconstruction was 51%, 49%, 23%, and 60.5%, respectively. The selection of the reconstruction material is individualized for each patient based on several patient, anatomical, and disease-specific factors, such as comorbidities, shape and size of the breast, availability of tissue around the breast and other donor sites, and planned adjuvant therapy. However, as presented in Fig. 1, we observed wide in-

https://doi.org/10.3857/roj.2020.00738

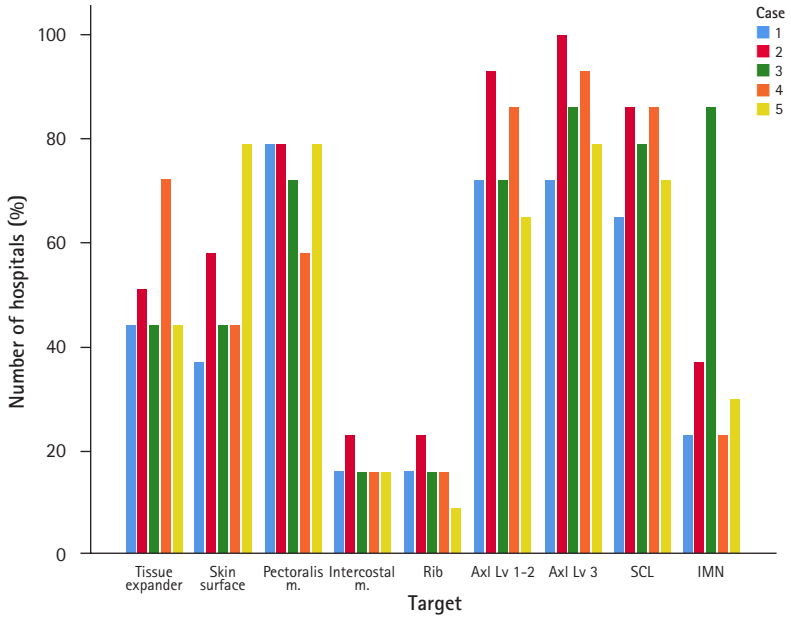


Fig. 4. Structures included in target volume delineation according to different clinical scenarios. AXL, axillary lymph node; SCL, supraclavicular lymph node; IMN, internal mammary node.

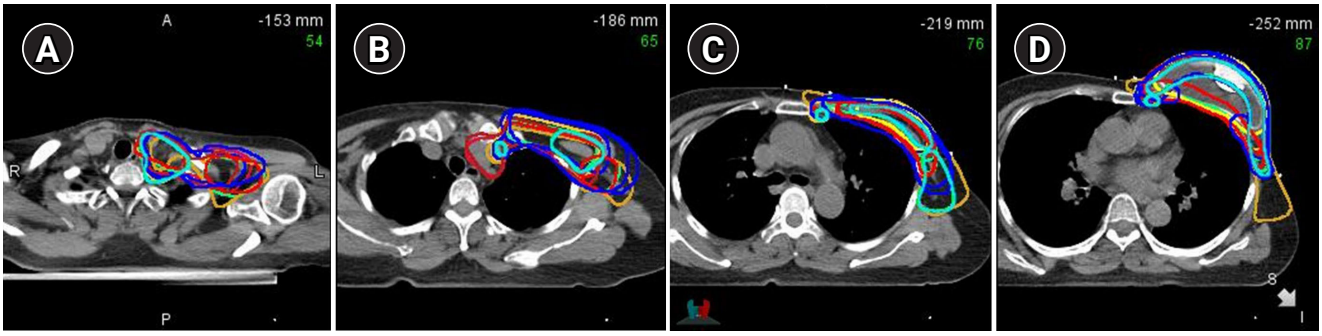


Fig. 5. Sum of all the radiation therapy structures included according to each clinical scenario. (A) Supraclavicular level. (B) Axillary level. (C) Upper reconstructed breast level. (D) Reconstructed breast level.

Table 4. Dose volume histograms in the same representative case

Variable	Value
PTV (mL)	563.67 (278.84–1,100.77)
Contralateral breast mean dose (Gy)	1.83 (0.03–9.48)
Skin Dmax (Gy)	47.95 (36.56–57.05)
Mean lung dose (Gy)	13.26 (5.33–18.80)
Mean heart dose (Gy)	5.08 (0.08–27.3)
LAD dose (Gy)	9.91 (0.08–32.06)
Lung V_5 (mL)	43.89 (16.35–99.45)
Lung V_{10} (mL)	38.21 (12.67–81.89)
Lung V_{20} (mL)	23.65 (6.70–34.03)

Values are presented as median (range).
PTV, planning target volume.

ter-hospital variability in the use of breast reconstruction material, which reflected that the hospital where a patient underwent the reconstruction dominantly influenced the decision-making regarding the same. Considering that the thickness of post-mastectomy spared skin flap is one of the major determinants of one-stage immediate reconstruction and the rate of reconstruction complications, the choice of breast reconstruction can also be affected based on whether a patient underwent skin-sparing mastectomy. According to a survey in the United States, implant-based reconstruction was highly utilized in the setting of bilateral mastectomy [14]. Similarly, there have been substantial developments in the use of implant-based techniques and decrease in the use of autologous reconstruction materials.

In the setting of prosthetic reconstruction, 87.9% of patients in the current study underwent partial deflation of the tissue expanders before RT and only 9.3% had full inflation during RT, which was in contrast to the practice patterns in the United States where 75.2% of the respondents specified that they do not routinely de-

flate the expander before RT [15]. Given that recent retrospective studies from Korea reported that maximal inflation status at the time of RT was significantly associated decreased risk of reconstruction-related complications [16], this issue needs to be discussed with reconstructive surgeons and investigated further in the future.

Interestingly, we found more heterogeneity in the details regarding radiation. Firstly, two-thirds of the patients were treated with conventional fractionation while a few large-volume hospitals preferred hypofractionation RT schedules with various regimens. Data supporting hypofractionation RT following mastectomy are still very limited, especially, when accompanied by breast reconstruction [17]. In 2019, we previously reported that hypofractionation RT (40 Gy in 15 fractions) may mitigate the risk of complications in two-stage prosthetic breast reconstruction [18]. Currently, several randomized trials—Alliance A221505 (NCT03414970), FABREC (NCT03422003)—are underway to investigate the role of hypofractionation RT in reconstructed breasts. Secondly, the use of boost RT was underutilized in the present cohort (15.6%) in contrast with a US survey in 2014, in which 66.5% of respondents indicated that they would prescribed boost RT [15]. A recent study from Harvard suggests that boost RT was significantly associated with reconstruction-related complications and reconstruction failure and that it does not improve local tumor control [19]; therefore, routine use of boost RT should be avoided and risk-to-benefit assessment is recommended. Bolus was applied in 53.5% of the patients, which is similar to the results of the US survey in which a majority of respondents (52.2%) stated that bolus is used in the setting of tissue expanders [15].

The most interesting finding of the present study is the startling variability in the target delineation and RT plans between physicians as well as clinical scenarios (Fig. 5; Supplementary Fig. S1). In contrast to field-based PMRT techniques, in volume-based RT planning, the variations in the target could significantly influence RT-related toxicities and/or oncological outcomes. In this context, the European Society for radiotherapy and Oncology–Advisory Committee in Radiation Oncology Practice (ESTRO–ACROP) presented multidisciplinary consensus-based target volume guidelines in the setting of PMRT after implant-based immediate reconstruction [20,21] that could play an important role in reducing the inter-physician variability.

There are several limitations to this study. First, the current study did not represent the whole population of Korea. Despite the best efforts, 16 institutions participated in this study and only six physicians completed the final submission for the dummy run study. Second, this cross-sectional study only included data of 2 years; therefore, a follow-up study is needed to identify further findings. Third, the data regarding reconstruction in patients who did not receive PMRT was lacking and, hence, the generalization of these findings to all breast reconstruction practices in Korea is limited. Reconstruction complications and their predictors will be discussed in another article.

In conclusion, in Korea, breast reconstruction has become an important consideration in the multidisciplinary management of patients with breast cancer due to the importance of the psychosocial functions of the symmetric breast mound. Our study's findings regarding the variability in reconstruction and PMRT details, therefore, provide valuable information to physicians and patients. As the reconstructive and therapeutic options become more sophisticated, this balance will be on the forefront of further cancer treatment. Multidisciplinary collaboration between radiation oncologists, surgical oncologists, plastic surgeons, and medical oncologists is imperative to deliver the best care to our patients. Our multi-center prospective observational study (NCT03523078) is underway to evaluate patient satisfaction and cosmetic outcomes according to breast reconstruction and different type of PMRT.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by the Research Grant of the Korean Foundation for Cancer Research (No. 2017-B-3).

Supplementary Materials

Supplementary materials can be found via http://doi.org/10.3857/roj.2020.00738

References

1. Panchal H, Matros E. Current trends in postmastectomy breast reconstruction. Plast Reconstr Surg 2017;140(5S):7S-13S.
2. Oh C, Winocour SJ, Lemaine V. Latest trends in subpectoral breast reconstruction. Semin Plast Surg 2019;33:224-8.
3. Nelson JA, Allen RJ Jr, Polanco T, et al. Long-term patient-reported outcomes following postmastectomy breast reconstruction: an 8-year examination of 3268 patients. Ann Surg 2019;270:473-83.
4. Ho TB, Wood WC, Mspt PD. Breast reconstruction in the setting of postmastectomy radiotherapy: controversies and disparities.

Oncology (Williston Park) 2019;33:688845.
5. Ho AY, Hu ZI, Mehrara BJ, Wilkins EG. Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. Lancet Oncol 2017;18:e742-e753.
6. Chawla AK, Kachnic LA, Taghian AG, Niemierko A, Zapton DT, Powell SN. Radiotherapy and breast reconstruction: complications and cosmesis with TRAM versus tissue expander/implant. Int J Radiat Oncol Biol Phys 2002;54:520-6.
7. Rozen WM, Ashton MW. Radiotherapy and breast reconstruction: oncology, cosmesis and complications. Gland Surg 2012;1:119-27.
8. Thamm OC, Andree C. Immediate versus delayed breast reconstruction: evolving concepts and evidence base. Clin Plast Surg 2018;45:119-27.
9. Xu F, Sun H, Zhang C, et al. Comparison of surgical complication between immediate implant and autologous breast reconstruction after mastectomy: a multicenter study of 426 cases. J Surg Oncol 2018;118:953-8.
10. Lemaine V, Schilz SR, Van Houten HK, Zhu L, Habermann EB, Boughey JC. Autologous breast reconstruction versus implant-based reconstruction: how do long-term costs and health care use compare? Plast Reconstr Surg 2020;145:303-11.
11. Jagsi R, Momoh AO, Qi J, et al. Impact of radiotherapy on complications and patient-reported outcomes after breast reconstruction. J Natl Cancer Inst 2018;110:157-65.
12. Min SY, Kim Z, Hur MH, et al. The basic facts of Korean Breast Cancer in 2013: results of a nationwide survey and breast cancer registry database. J Breast Cancer 2016;19:1-7.
13. Kang SY, Kim YS, Kim Z, et al. Breast cancer statistics in Korea in 2017: data from a breast cancer registry. J Breast Cancer 2020;23:115-28.
14. Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in U.S. breast reconstruction: increasing implant rates. Plast Reconstr Surg 2013;131:15-23.
15. Thomas K, Rahimi A, Spangler A, Anderson J, Garwood D. Radiation practice patterns among United States radiation oncologists for postmastectomy breast reconstruction and oncoplastic breast reduction. Pract Radiat Oncol 2014;4:466-71.
16. Woo KJ, Paik JM, Bang SI, Mun GH, Pyon JK. The impact of expander inflation/deflation status during adjuvant radiotherapy on the complications of immediate two-stage breast reconstruction. Aesthetic Plast Surg 2017;41:551-9.
17. Smith NL, Jethwa KR, Viehman JK, et al. Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: Initial report of reconstruction outcomes and predictors of complications. Radiother Oncol 2019;140:76-83.
18. Chang JS, Song SY, Oh JH, et al. Influence of radiation dose to reconstructed breast following mastectomy on complication in breast cancer patients undergoing two-stage prosthetic breast reconstruction. Front Oncol 2019;9:243.
19. Naoum GE, Salama L, Ho A, et al. The impact of chest wall boost on reconstruction complications and local control in patients treated for breast cancer. Int J Radiat Oncol Biol Phys 2019;105:155-64.
20. Kaidar-Person O, Vrou Offersen B, Hol S, et al. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol 2019;137:159-66.
21. Mutter RW. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol 2019;141:329-30.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):244-252
https://doi.org/10.3857/roj.2020.00850

Prognostic significance of lymph node ratio after neoadjuvant chemoradiation therapy for esophageal squamous cell carcinoma

Jeong Yun Jang[1], Jesang Yu[1], Kye Jin Song[1], Yoon young Jo[1], Ye Jin Yoo[1], Sung-Bae Kim[2], Sook Ryun Park[2], Young-Hee Kim[3], Hyeong Ryul Kim[3], Jong Hoon Kim[1]

[1]*Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[2]*Department of Medical Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*
[3]*Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea*

Received: October 16, 2020
Revised: November 17, 2020
Accepted: November 18, 2020

Correspondence:
Jong Hoon Kim
Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-5680
Fax: +82-2-3010-6950
E-mail: jhkim2@amc.seoul.kr
ORCID:
https://orcid.org/0000-0001-9002-1195

Purpose: We retrospectively evaluated the prognostic significance of lymph node ratio (LNR) in patients with esophageal squamous cell carcinoma who underwent neoadjuvant concurrent chemoradiation therapy (NCRT) followed by surgery.

Materials and Methods: In total, 270 patients who underwent NCRT followed by surgery between August 2005 and December 2015 were included. They were divided into three groups: LNR 0 (n = 196), LNR low (0 < LNR ≤ 0.1; n = 63), and LNR high (>0.1; n = 11). The primary endpoint was overall survival (OS), and the secondary endpoints were freedom from local recurrence (FFLR), distant metastasis-free survival (DMFS), and disease-free survival (DFS).

Results: The median number of retrieved lymph nodes per patient was 33. Pathologically, 74 patients had positive lymph nodes. The median follow-up duration was 36.1 months, and the median survival period was 68.4 months. There was a significant correlation between LNR and the number of positive lymph nodes (correlation coefficient = 0.763, p < 0.001). There was a substantial difference in the OS among the LNR groups, with 2-year survival rates of 79.0%, 54.0%, and 9.1% in the LNR 0, LNR low, and LNR high groups, respectively (p < 0.001). A marked decrease in FFLP, DMFS, and DFS was observed with the increasing LNR. In subgroup analysis, the survival results of patients with clinically positive lymph node were similar from those of entire cohort.

Conclusion: LNR is a significant prognostic factor in patients with esophageal squamous cell carcinoma who underwent NCRT followed by surgery. Additional treatment and closer follow-up would be necessary for patients with a high LNR.

Keywords: Esophageal squamous cell carcinoma, Radiotherapy, Lymph node ratio, Prognosis

Introduction

Esophageal cancer has the seventh highest incidence rate and 6th highest mortality rate among all type of cancer worldwide, accounting for 1 of 20 cancer deaths in 2018 [1]. Despite advancement in the staging system and treatment techniques for esophageal cancer such as surgery, chemotherapy, and radiation therapy, its overall survival (OS) rate is low [2].

Among various prognostic factors, not only the presence of lymph node metastasis, but also the number of lymph node metastases is important, and its significance was reflected in staging systems of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in 2009 [3-5]. In addition, many studies have reported that the number of lymph

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

nodes removed during surgery was a significant factor affecting the prognosis of patients [6,7]. Hence, the concept of lymph node ratio (LNR), the ratio of the number of positive lymph nodes to the total number of removed lymph nodes, has gained attention as an important prognostic factor in gastrointestinal cancers including esophageal cancer [8-13]. However, studies on LNR in squamous cell carcinoma (SqCC) are relatively rare, as the majority of the studies were conducted in Western countries where adenocarcinoma is the dominant histology. In addition, these studies have limitations in the heterogeneity of treatment methods and absence of a subgroup analysis. Hence, it may not be appropriate to apply LNR reported in previous studies to the current clinical conditions.

Therefore, this study aimed to investigate the importance of LNR as a prognostic factor in patients with esophageal squamous cell carcinoma who underwent neoadjuvant concurrent chemoradiation therapy (NCRT) followed by surgery.

Materials and Methods

1. Patients

We retrospectively reviewed the medical records of patients who underwent NCRT at Asan Medical Center between August 2005 and December 2015. All patients underwent surgery after NCRT, and the pathological results were confirmed. The exclusion criteria were as follows: patients with double primary cancer within 5 years before the diagnosis of esophageal cancer, those with histology other than SqCC, those with distant metastases at the time of diagnosis, those receiving a radiation dose of <36 Gy, and those with a short follow-up period after surgery (<3 months). In total, 270 patients were enrolled in this study; all patients had undergone esophagogastroduodenoscopy (EGD) with biopsy, endoscopic ultrasonography (EUS), chest computed tomography (CT), and positron emission tomography-computed tomography (PET-CT) for appropriate staging. The informed consent was waived.

2. Treatments and follow-up

All patients were administered XP, FP, or oxaliplatin/TS-1 chemotherapy as NCRT. In the XP regimen, patients received capecitabine 1,600 mg/m^2/day for 5 days plus cisplatin 30 mg/m^2/day on the first day, weekly. In the FP regimen, patients received cisplatin 60 mg/m^2/day on the first day plus 5-fluorouracil 1,000 mg/m^2/day on the second day for 4 days, every 3 weeks. In the oxaliplatin/TS-1 regimen, patients received TS-1 50 mg orally twice a day daily during the whole period of concurrent chemoradiation therapy, and oxaliplatin 130 mg/m^2 as an intravenous infusion on day 1, repeated every 3 weeks. The median dose of radiation therapy was 46 Gy (range, 38 to 50.4 Gy), and the fraction size was either 180 cGy or 200 cGy. Since the aim of radiotherapy was neoadjuvant treatment, elective nodal irradiation was used in most cases, and the range of field was customized according to the locations of the primary lesion and metastatic lymph nodes. EGD, chest CT, and PET-CT were used to evaluate tumor response and absence of new metastasis at 1 month after NCRT before proceeding with surgery. All surgeries were performed by expert surgeons with experience in performing >50 radical esophagectomies per year. The median interval between the last day of NCRT and surgery was 8 weeks. In total, 65.9% patients underwent Ivor–Lewis operation and 34.1% patients underwent McKeown operation, and a sufficient number of lymph nodes were retrieved to evaluate the post-treatment pathological stage according to the AJCC 7th edition [14]. We derived LNR and classified patients into three groups: LNR 0, LNR low ($0 <$ LNR ≤ 0.1), and LNR high (>0.1).

All patients were regularly followed up by a radiation oncologist, medical oncologist, and thoracic surgeon. At each follow-up, history taking, physical examination, and blood tests (complete blood count and blood biochemistry tests) were performed. Chest CT and abdominal and pelvic CT, if needed, were performed every 6 months for 2 years and annually for 5 years. EGD was performed every year, and biopsy was performed selectively only when tumor recurrence was suspected. PET-CT was not mandatory and was performed only when tumor recurrence was suspected.

3. Outcomes and statistical analysis

The primary endpoint was OS, and the secondary endpoints were freedom from local recurrence (FFLR), distant metastasis-free survival (DMFS), and disease-free survival (DFS). Statistical analyses were performed using SPSS version 22.0 (IBM SPSS, Armonk, NY, USA). Pearson correlation analysis was performed to determine the correlation between LNR and the number of positive lymph nodes. Univariate analysis was performed through logistic regression analysis, and a Cox proportional hazard model was used for multivariate analysis to find prognostic risk factors. The Kaplan–Meier method was used to derive the survival outcome.

Results

1. Patients and treatments

A total of 270 patients were included, and their characteristics are presented in Table 1. The median age was 63 years (range, 42 to 76 years), and 94.4% patients were men. Tumors were confirmed by endoscopic biopsy before initiating treatment. All patients were diagnosed with SqCC. Tumor location was categorized into the upper, mid-, and lower thoracic esophagus by measuring the distance from the upper incisor to the tumor epicenter using endoscopic

Table 1. Patients' characteristics

Characteristic	LNR				p-value
	0 (n = 196)	Low (n = 63)	High (n = 11)	Total (n = 270)	
Age (yr)	63 (42–76)	59 (52–73)	159 (56–75)	63 (42–76)	0.059
Sex					0.696
Male	185 (94.4)	59 (93.6)	11 (100)	255 (94.4)	
Female	11 (5.6)	4 (6.4)	0 (0)	15 (5.6)	
Tumor differentiation					0.231
Well	30 (15.3)	2 (3.2)	2 (18.2)	34 (12.6)	
Moderately	143 (73.0)	7 (11.1)	8 (72.7)	204 (75.6)	
Poor	16 (8.2)	53 (84.1)	1 (9.1)	24 (8.9)	
Not checkable	7 (3.6)	1 (1.6)	0 (0)	8 (3.0)	
Tumor location[a)]					0.449
Upper	24 (12.2)	10 (15.9)	1 (9.1)	35 (13.0)	
Middle	100 (51.0)	22 (35.0)	6 (54.5)	128 (47.4)	
Lower	72 (36.7)	31 (49.2)	4 (36.4)	107 (39.6)	
Initial clinical stage					0.033
I	17 (8.7)	8 (12.7)	1 (0.9)	26 (9.6)	
II	57 (29.1)	17 (27.0)	0 (0)	74 (27.4)	
III	117 (59.7)	31 (49.2)	9 (81.8)	157 (58.1)	
IV	4 (2.0)	7 (11.1)	1 (0.9)	12 (4.4)	
Clinical T stage					0.167
cT1	21 (10.7)	8 (12.7)	1 (9.1)	30 (11.1)	
cT2	58 (29.6)	23 (36.5)	1 (9.1)	82 (30.4)	
cT3	115 (58.7)	29 (46.0)	9 (81.8)	153 (56.7)	
cT4	2 (1.0)	3 (4.8)	0 (0)	5 (1.9)	
Clinical N stage					< 0.001
Positive	131 (66.8)	58 (92.1)	9 (81.8)	198 (73.3)	
Negative	65 (33.2)	5 (7.9)	2 (18.2)	72 (26.7)	
LNs examined	33 (8–69)	36 (13–67)	21 (6–33)	33 (6–69)	0.582
LNs positive	0 (0–0)	1 (1–4)	4 (2–8)	0 (0–8)	< 0.001
Chemotherapy					
XP	152 (77.6)	48 (76.2)	10 (90.9)	210 (77.8)	0.668
FP	3 (1.5)	0 (0)	0 (0)	3 (1.1)	
Oxaliplatin/TS-1	41 (20.9)	15 (23.8)	1 (9.1)	57 (21.1)	
Operation					0.932
Ivor–Lewis operation	131 (66.8)	40 (63.5)	7 (63.6)	178 (65.9)	
McKeown operation	65 (33.2)	23 (36.5)	4 (36.4)	92 (34.1)	

Values are presented as median (range) or number (%). Because of rounding, not all percentages total 100.
LNR, lymph node ratio; LN, lymph node; XP, capecitabine/cisplatin; FP, 5-fluorouracil/cisplatin.
[a)]Classification by measuring the distance from the upper incisor (UI) to the tumor by esophagogastroscopy (upper, UI 20–25 cm; mid, UI 25–30 cm; and lower, 30–40 cm).

evaluation and other imaging studies. Approximately half of the patients had lesions in the mid-thoracic esophagus, and upper thoracic esophageal cancer was the least. Most patients had advanced stage disease, for which NCRT and surgery were recommended as the standard treatment [15]. However, some patients had early-stage disease. Clinically suspected lymph nodes were found in 73.3% patients.

2. Correlation between LNR and the number of positive lymph node

In 270 patients, a total of 9,150 lymph nodes were removed during surgery, of which 128 (1.4%) were identified as metastatic nodes. The median number of lymph nodes harvested per person during surgery was 33 (range, 8 to 69). Pearson correlation analysis showed that there was a significant correlation between LNR and the number of metastatic lymph nodes (correlation coefficient =

https://doi.org/10.3857/roj.2020.00850

0.763, p < 0.001) (Fig. 1).

3. OS, LCR, DFS, and DMFS according to LNR

The median follow-up period was 36.1 months (range, 5.3 to 164 months). In the entire study cohort, the median OS time was 68.4 months (range, 5.3 to 172.2 months) and the 2- and 5-year OS rate were 70.2% and 52.4%, respectively. Table 2 shows the survival outcomes in all study groups. The median survival period according to LNR was 81.2 months in the LNR 0 group, 35.6 months in the LNR low group, and 11 months in the LNR high group (p < 0.001). The 2- and 5-year survival rates in the LNR 0, low, and high groups were 79.0%, 54.0%, and 9.1% and 60.2%, 37.6%, and 0.0%, respectively (p < 0.001) (Fig. 2A). Four variables (initial clinical stage, clinical nodal stage, pathologic nodal stage, and LNR) had prognostic significance on Cox regression analysis for OS (Table 3).

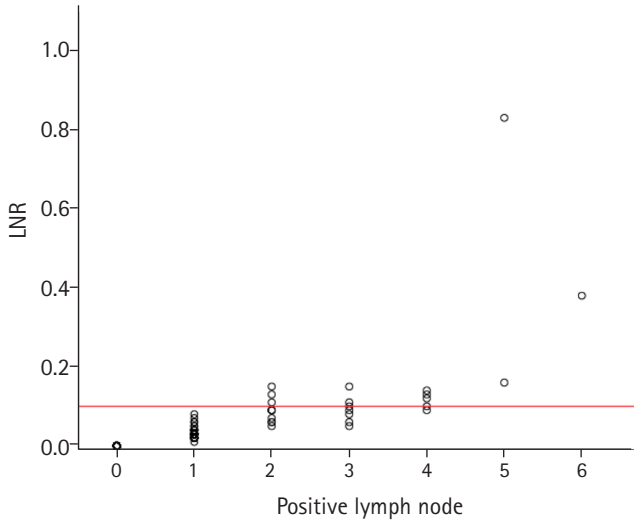


Fig. 1. Correlation between lymph node ratio (LNR) and the number of positive lymph node.

Local recurrence occurred in 59 patients (21.9%), distant metastasis occurred in 49 patients (18.1%), and both local recurrence and distant metastasis occurred in 29 patients (10.7%). Local recurrence rates were 16.3%, 33.3%, and 54.5% in the LNR 0, LNR low, and LNR high groups, respectively.

The 5-year FFLR, DMFS, and DFS rates in the entire study cohort were 76.0%, 78.5%, and 68.1%, respectively. The 5-year FFLR, DMFS, and DFS rates were significantly different among all three LNR groups, respectively; the smaller the LNR value, the better the survival rate (Fig. 2B–2D).

The 2-year DMFS rates in the LNR 0, low, and high groups were 91.6%, 78.1%, and 0.0%, respectively, showing significant differences among the groups. The difference was more prominent between the LNR high group and the other groups (p < 0.001) than that between the LNR 0 and LNR low groups (p = 0.044) (Fig. 2C). Of the 11 patients with high LNR, 3 patients had lung metastasis, 1 patient had liver metastasis, and 1 patient had multiple lymph node metastases.

The same analyses were performed in the subgroup of patients in whom positive lymph node was diagnosed on EUS or CT before NCRT. The results of subgroup were similar from those of entire cohort (Table 4). There were 198 patients (73.3%) with clinical node positive, of which 126 patients expired. Median OS was 48.3 months, about 20 months shorter compared to the OS for the entire cohort. Their median OS was 75.1 months, 34.8 months, and 10.3 months for LNR 0, low, and high, respectively, and a lower

Table 2. The survival outcomes according to LNR

	LNR	Median survival time (mo)			2-yr survival rate (%)	p-value
		Kaplan-Meier estimate	95% confidence limits			
			Lower	Upper		
OS	0	81.2	51.6	110.8	79.0	< 0.001
	Low	35.6	14.8	56.4	54.0	
	High	11.0	6.9	15.1	9.1	
FFLR	0	N/R	-	-	85.9	< 0.001
	Low	N/R	-	-	69.7	
	High	13.2	8.4	18	0.0	
DMFS	0	N/R	-	-	91.6	< 0.001
	Low	N/R	-	-	78.1	
	High	17.1	4.5	29.7	0.0	
DFS	0	N/R	-	-	80.1	< 0.001
	Low	N/R	-	-	61.2	
	High	8.6	3.7	13.5	0.0	

OS, overall survival; FFLR, free from local recur; DMFS, distant metastasis-free survival; DFS, disease-free survival; LNR, lymph node ratio; N/R, not reached.

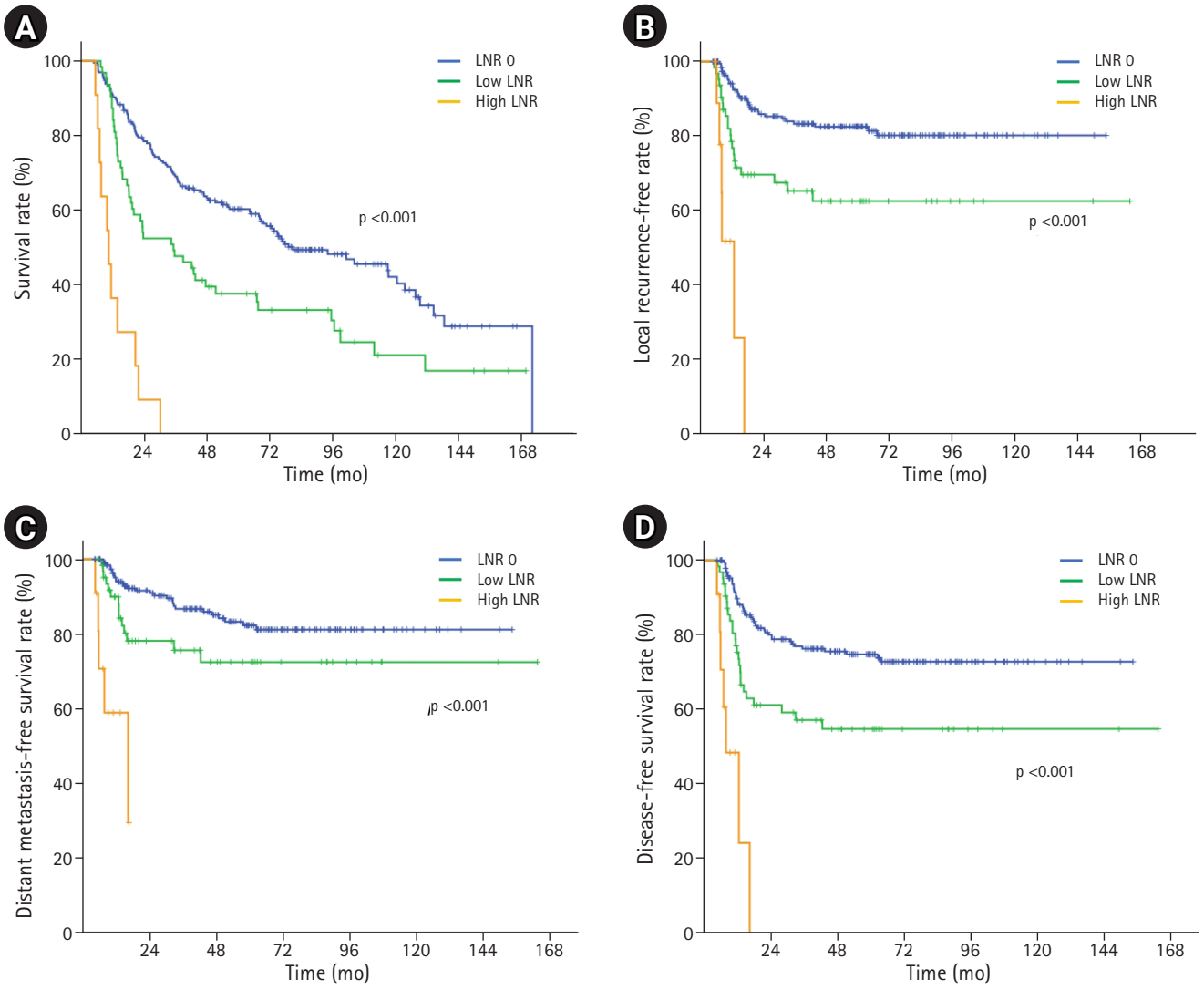


Fig. 2. The survival outcomes according to lymph node ratio (LNR): (A) overall survival rate, (B) local recurrence-free rate, (C) distant metastasis-free survival rate, and (D) disease-free survival rate.

survival rate was shown in the group with a large LNR value, as in all patients ($p < 0.001$). In addition, FFLR, DMFS, and DFS values also showed significant differences among all three LNR groups, confirming a low survival rate in the high LNR group.

As another subgroup analysis, patients were divided by pathologic N stages. In ypN0 patients, we tried to determine the difference in survival according to clinical nodal status, and in patients with positive pathologic lymph node, we tried to find out the difference according to the LNR values. First, there were a total of 196 patients with ypN0, of which 65 and 131 patients were clinical node negative and positive, respectively. The 2-year OS rate was statistically higher in patients with negative clinical nodal status with 89.1% ($p = 0.017$). However, there were no significant differences in FFLR, DMFS, and DFS between two groups (Supplementary Table S1). Patients with positive pathologic nodal status were classified into ypN1, N2, and N3, and the numbers were 59, 14, and 1, respectively. Due to the small number of patients in ypN3 stage, the analysis was performed in two groups, ypN1 and ypN2-3. In ypN1, patients with low LNR showed better survival in all except DMFS. The median OS for high LNR and low LNR showed a difference of about five times at 14.3 months and 69.3 months ($p = 0.008$). However, in the ypN2-3 group, there was no significant difference between the low LNR and the high LNR patients in any survival outcome (Supplementary Table S2).

Discussion and Conclusion

In this study, we found that LNR is a significant prognostic factor associated with OS. It is difficult to directly compare most previous studies with the current study because they included patients who

https://doi.org/10.3857/roj.2020.00850

Table 3. Univariate and multivariate analysis for overall survival (n = 270)

Variable	No. of patients	Univariate analysis		Multivariate analysis		
		2-yr survival rate (%)	p-value	HR	95% CI	p-value
Age (yr)			0.167			
≤ 63	164	68.9				
> 63	106	72.3				
Sex			0.338			
Male	255	70.4				
Female	15	66.7				
Tumor differentiation			0.597			
Well	24	82.4				
Moderately	204	66.5				
Poor	24	83.3				
Not checkable	8	75.0				
Tumor location[a]			0.933			
Upper	34	70.6				
Middle	128	70.3				
Lower	108	69.8				
Initial clinical stage			0.001			0.011
I	26	92.3		1	Referent	
II	74	78.3		1.739	1.206–2.506	
III	157	62.9		8.15	4.203–15.802	
IVa	13	69.2		1.599	1.067–2.397	
Clinical nodal stage			0.003			0.023
Positive	198	65.1		1	Referent	
Negative	72	84.6		1.599	10.67–2.397	
Pathological nodal stage[b]			< 0.001			
ypN0	196	79.0				
ypN1	59	55.9				
ypN2-3	15	13.3				
LNs examined			0.726			
≤ 15	13	53.8				
> 15	257	71.1				
LNR			< 0.001			< 0.001
0	196	79.0		1	Referent	
Low (> 0 and ≤ 0.1)	63	54.0		1.739	1.206–2.506	
High (> 0.1)	11	9.1		8.15	4.203–15.802	
Chemotherapy			0.572			
XP	210	69.4				
FP	3	66.7				
Oxaliplatin/TS-1	57	76.9				
Operation			0.827			
Ivor–Lewis operation	178	69.4				
McKeown operation	92	73.3				

HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio; LN, lymph node; XP, capecitabine/cisplatin; FP, 5-fluorouracil/cisplatin.
[a]Classification by measuring the distance from the upper incisor (UI) to the tumor by Esophagogastroscopy (upper, UI 20–25 cm; mid, UI 25–30 cm; lower, 30–40 cm).
[b]Due to strong linear relationship between the pathologic N stage and LNR, only LNR was included in the multivariate analysis.

Table 4. The survival outcomes according to LNR for patients with clinically positive lymph node

	LNR	Median survival time (mo)			2-yr survival rate (%)	p-value
		Kaplan-Meier estimate	95% confidence limits			
			Lower	Upper		
OS	0	75.1	62.9	87.3	74.0	<0.001
	Low	34.8	15.5	54.1	53.4	
	High	10.3	3.9	16.7	11.1	
FFLR	0	N/R	-	-	82.1	<0.001
	Low	N/R	-	-	67.3	
	High	8.6	7.6	9.6	0.0	
DMFS	0	N/R	-	-	89.2	0.001
	Low	N/R	-	-	79.9	
	High	8.6	-	-	47.6	
DFS	0	N/R	-	-	75.9	<0.001
	Low	N/R	-	-	61.4	
	High	8.6	6.2	11.0	0.0	

OS, overall survival; FFLR, free from local recur; DMFS, distant metastasis-free survival; DFS, disease-free survival; LNR, lymph node ratio; N/R, not reached.

received inhomogeneous treatment (NCRT followed by surgery and surgery alone cases together), had inhomogeneous histology (both adenocarcinoma and SqCC together), or had inhomogeneous stages. For example, in the study conducted by Nigro et al. [10], all patients had adenocarcinoma and they were assigned only to the surgery group. In the study by Bollschweiler et al. [3], approximately half of the patients had SqCC and the other patients had adenocarcinoma; 62% patients were included the surgery alone group. However, the study by Wilson et al. [12] included a more homogeneous patient group in which >80% patients had SqCC and most patients underwent NCRT. However, the median OS was 22 months, and the 5-year survival rate was 27%, which was slightly lower than the expected values. Compared with the study by Liu et al. [13] that enrolled SqCC in near 100%, their median OS was 36.7 months, which was very similar to that of 36.1 months in our study. From the above studies, we could draw a very reasonable conclusion that there is a significant correlation between LNR and survival, and the higher the LNR, the lower the survival rate.

In our study, the distribution of patient characteristics in each group was quite even, except initial clinical stage and clinical node status; however, uneven distribution of clinically positive lymph nodes could have affected the survival outcome. Hence, we performed subgroup analysis in patients with clinically positive lymph node. In this subgroup, we could confirm that not only the OS but also the tendency of local recurrence and distant metastasis were repeated, which is the same as the results of entire cohort patients. Therefore, we can conclude that LNR is a significant prognostic factor regardless of the clinical nodal status.

In addition, we have questioned how much LNR means when only patients within the same pathologic stage are studied. Therefore, another subgroup analysis was performed for patients with ypN1 and ypN2-3 by dividing them into low LNR and high LNR groups. In the ypN1 group, low LNR patients showed better outcomes in OS, FFLR, and DFS. Through this, we found that the survival difference was shown according to the LNR value even within the same pathologic stage. Consequently, not only positive lymph node but also LNR with the consideration of the number of removed lymph node could provide additional information in predicting the patient's prognosis. However, since the number of each LNR subgroup is not sufficient, an analysis including a larger number of patients to confirm the results of this study is necessary. On the other hand, in patients with ypN2-3, there was no significant difference in survival outcomes according to the LNR value. It can be interpreted that LNR does not act as a prognostic factor within this stage, but this result may have been derived because the number of patients is extremely small in both high LNR and low LNR groups. Therefore, it will be difficult to assert that LNR has no meaning in patients with high pathologic N stage based on this result alone. Therefore, we expect that this also could have resulted in significant results if the study had enough patients.

Of course, as can be seen through the univariate analysis of this study, the clinical and pathologic stage established by AJCC are one of the major risk factors that have a very large influence on the prognosis of patients. Since LNR is the proportion of the number of positive lymph node to the number of retrieved lymph node, it can be readily deduced that it will correlate with the number of metastatic lymph node, which is a well-known risk factor. However, the number of dissected lymph node, which is the denominator, is also

 https://doi.org/10.3857/roj.2020.00850

a key element in the formula for calculating the LNR, so it would be difficult to say that there is always a correlation between two variables. Therefore, an analysis was conducted, and a distinct positive correlation was proved. Despite this result, when univariate and multivariate analyses were performed, LNR itself was found to be a prognostic factor for survival. For this reason, in addition to clinical and pathological stages, it will also be necessary to focus on the LNR value, which is emerging as another prognostic factor. Consequently, patients with high LNR values need more careful observation, and early detection of recurrence followed by salvage treatment is more needed than in the other patients.

Another important issue is setting the criteria for "high LNR" and we do not have enough data to make a consensus on that specific value. Many studies have used different cutoff values such as 0.1, 0.2, 0.25, or 0.5. In the study by Bollschweiler et al. [3], there was a significant difference in survival when the LNR value was >0.2 ($p < 0.01$), and in the study by Nigro et al. [10], there was a significant difference in survival when the LNR value was 0.1. A literature review revealed that the LNR value that determines significance decreases with the increasing number of the total retrieved lymph node [3,10,12]. In this study, the median number of lymph nodes harvested per person was 33, and we set the cutoff value as low as 0.1. Therefore, LNR was divided into three groups according to this cutoff value, and a substantial proportion of patients belonged to the LNR 0 group due to the high ypCR rate in patients with SqCC. Initially, we enrolled 198 patients clinically positive lymph nodes at the time of diagnosis, and 131 of them showed complete response pathologically in nodal status after NCRT, accounting for 66% of the total ypN0 rate. Therefore, recruiting enough number of patients with high LNR in a single institution was challenging and we would like to say it requires multi-institutional cooperation. In this context, we agree that there was a limitation to determine a cutoff value based only on this study, even if we found significant differences in the survival rate based on the LNR value of 0.1.

Despite this limitation, we believe this study is meaningful as we recruited patients treated with the current standard treatment. Our study is not the first to show the importance of LNR as a prognostic factor, but we can say our results are based on homogeneous data from NCRT and surgery. Second, all of our patients were diagnosed as SqCC, which is dominant in Asian countries and its nature is different from adenocarcinoma. Third, consistency in treatment and follow-up was ensured by the multidisciplinary approach team consensus.

We believe that our results provided data regarding the current clinical situation, and hope it will be a basis for future prospective studies including a large number of patients and considering additional treatment for patients with high LNR.

Conflict of Interest

No potential conflict of interest was reported by the authors.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2020.00850.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Egyud MR, Tseng JF, Suzuki K. Multidisciplinary therapy of esophageal cancer. Surg Clin North Am 2019;99:419-37.
3. Bollschweiler E, Baldus SE, Schroder W, Schneider PM, Holscher AH. Staging of esophageal carcinoma: length of tumor and number of involved regional lymph nodes. Are these independent prognostic factors? J Surg Oncol 2006;94:355-63.
4. Hofstetter W, Correa AM, Bekele N, et al. Proposed modification of nodal status in AJCC esophageal cancer staging system. Ann Thorac Surg 2007;84:365-75.
5. Rice TW, Rusch VW, Ishwaran H, Blackstone EH; Worldwide Esophageal Cancer Collaboration. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer 2010;116:3763-73.
6. Peyre CG, Hagen JA, DeMeester SR, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248:549-56.
7. Altorki NK, Zhou XK, Stiles B, et al. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 2008;248:221-6.
8. Marchet A, Mocellin S, Ambrosi A, et al. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. Ann Surg 2007;245:543-52.
9. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005;23:8706-12.
10. Nigro JJ, DeMeester SR, Hagen JA, et al. Node status in transmural esophageal adenocarcinoma and outcome after en bloc

esophagectomy. J Thorac Cardiovasc Surg 1999;117:960-8.
11. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Ann Surg 2008;247:365-71.
12. Wilson M, Rosato EL, Chojnacki KA, et al. Prognostic significance of lymph node metastases and ratio in esophageal cancer. J Surg Res 2008;146:11-5.
13. Liu YP, Ma L, Wang SJ, et al. Prognostic value of lymph node metastases and lymph node ratio in esophageal squamous cell carcinoma. Eur J Surg Oncol 2010;36:155-9.
14. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-4.
15. Shapiro J, van Lanschot JJ, Hulshof MC, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-8.

https://doi.org/10.3857/roj.2020.00850

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):253-261
https://doi.org/10.3857/roj.2020.00472

Prospective evaluation of fiducial marker placement quality and toxicity in liver CyberKnife stereotactic body radiotherapy

Debnarayan Dutta[1], Kaushik Jagannath Kataki[1], Shibu George[2], Sruthi K. Reddy[1], Ajay Sashidharan[1], Rajesh Kannan[2], Ram Madhavan[1], Haridas Nair[1], Tushar Tatineni[1], Raghavendra Holla[3]

[1]*Department of Radiation Oncology, Amrita Institute of Medical Science, Kochi, India*
[2]*Department of Radiology, Amrita Institute of Medical Science, Kochi, India*
[3]*Department of Medical Physics, Amrita Institute of Medical Science, Kochi, India*

Received: July 15, 2020
Revised: September 23, 2020
Accepted: September 28, 2020

Correspondence:
Debnarayan Dutta
Department of Radiation Oncology, Amrita Institute of Medical Science, Kochi, India.
Tel: +91-9884234290
E-mail: duttadeb07@gmail.com
ORCID:
https://orcid.org/0000-0002-1513-391X

Background: Evaluate morbidities and "quality" of fiducial marker placement in primary liver tumours (hepatocellular carcinoma [HCC]) for CyberKnife.

Materials and Methods: Thirty-six HCC with portal vein thrombosis (PVT) were evaluated for "quality" of fiducial placement, placement time, pain score, complications, recovery time and factors influencing placement.

Results: One hundred eight fiducials were placed in 36 patients. Fiducial placement radiation oncologist score was "good" in 24 (67%), "fair" in 4 (11%), and "poor" in 3 (8%) patients. Concordance with radiologist score in "poor", "fair", and "good" score was 2/2 (100%), 4/5 (80%), and 24/27 (89%), respectively (p=0.001). Child-Pugh score (p=0.080), performance status (PS) (p=0.014) and accrued during "learning curve" (p=0.013) affected placement score. Mean placement time (p=0.055), recovery time (p=0.025) was longer and higher major complications (p=0.009) with poor PS. Liver segment involved (p=0.484) and the Barcelona Clinic Liver Cancer (BCLC) stage did not influence placement score. "Good" placement score was 30% in first cohort whereas 93% in last cohort (p=0.023). Time for placement was 42.2 and 14.3 minutes, respectively (p=0.069). Post-fiducial pain score 0–1 in 26 patients (72%) and pain score 3–4 was in 2 (6%). Five patients (14%) admitted in "day-care" (2 mild pneumothorax, 3 pain). Mortality in 1 patient (3%) admitted for hemothorax.

Conclusion: Fiducial placement is safe and in experienced hands, "quality" of placement is "good" in majority. Major complications and admission after fiducial placement are rare. Complications, fiducial placement time, recovery time is more during the "learning curve". Poor Child-Pugh score, extensive liver involvement, poor PS have higher probability of complications.

Keywords: Hepatocellular carcinoma, Stereotactic body radiotherapy, Fiducial marker

Introduction

Fiducial placement in liver tumours (hepatocellular carcinoma [HCC]) for robotic radiosurgery (CyberKnife) treatment is considered crucial step of treatment and also associated with morbidities [1]. In fact, fiducial placement is considered essential in both robotic radiosurgery (CyberKnife) and linac-based stereotactic body radiotherapy (SBRT) treatment. Fiducial markers for SBRT are generally introduced under percutaneous ultrasound or computed tomography (CT) guidance [2-4]. However, fiducial placement has it's own issues and need to be addressed [5]. It leads to a delay in treatment. Many clinicians will impose up to a 1-week delay from fiducial placement to treatment planning in order to allow the markers to "settle" [6]. The fiducial placement procedure is also as-

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

sociated with potential risks and complications like pain, vasovagal attack, pneumothorax, hemothorax, perforation of non-target organs, bile peritonitis, infection, hemobilia, neuralgia, and tumor seeding [7,8]. "Ideal" fiducial placement means appropriately placed fiducials, neither too close nor too far from each other and close to the target. Apart from these placement related parameters, clinical parameters such as time for placement, recovery time, pain score after placement, are also critical [9]. "Quality" of placement is a combination of mechanical parameters as per fiducial placement and also clinical parameters related to the placement. Unfortunately, though there are specifications for an "ideal" placement of fiducials, there is no published parameter for "quality" of fiducial placement.

The literature on fiducial related complications and migration related parameters from Indian subcontinent is very scarce [10]. Compliance, acceptability and pain related issues may not be similar in the Indian population as observed in Western population [10]. There is no well-known prospective study looking into the actual rate of fiducial migration, accuracy of fiducial placement and its utility in treatment planning, pain score and procedure related parameters. There are also no standard guidelines for the amount of fiducial migration expected and hence the time required to start the treatment and this needs further evaluation. Our present prospective study is to evaluate the feasibility and accuracy of fiducial placement under image guidance and to evaluate the fiducial placement score, pain score, fiducial placement related complications and impact of fiducial placement on planning and treatment. The migration within liver during treatment (intra-treatment migration) related parameters were analyzed in separate manuscript due to space constraint.

Materials and Methods

Between one calendar year (Mar 2017–Mar 2018), 108 fiducial placements done in 36 primary liver tumours (HCC) and were accrued in the present Amrita Institute of Medical Science Institutional Ethical & Scientific Committee approved prospective observational study for robotic radiosurgery treatment (No. AIMS-2018 ONCO-124). Patients were accrued after obtaining consent in native language. All these patients were radiologically diagnosed HCC, have preserved liver function (bilirubin < 4 mg/dL, platelet > 75,000, international normalized ratio [INR] < 2) and good performance status (PS 0–1 or early PS 2). All the patients underwent three specified fiducials place in the liver under either CT scan or ultrasound-guided. Fiducials were placed by radiologist with an ideal situation where the fiducials will be in equidistance from each other (max distance 5 cm and min distance 2 cm) and the angles between the fiducials are specified. Quality of fiducial placement as per the radiologist and treating radiation oncologist were assessed by institution defined parameters (Table 1). Placement time, pain score, complications, recovery time and factors influencing fiducial placement were analyzed. Demographic profiles of the patients are in Table 2.

1. Image guided fiducial placement and simulation

Fiducial placement was done under computed tomographic (SOMATOM Emotion 16 slice CT; Siemens, Erlangen, Germany) or ultrasonographic (Philips iU22 ultrasound; Philips Medical System, Cleveland, OH, USA) guidance under sterile conditions by an interventional radiologist (SG) in the presence of radiation oncologist (DD) to guide the placement of the fiducials. Three gold fiducials were inserted percutaneously under image guidance using a cylindrical 20-cm long 18-gauge puncture needle with a preloaded fiducial marker [11,12]. Each fiducial is a cylinder made from 99% pure gold with whorl on the surface. It weighs 17 gm and has a size of 1.2 mm × 5.0 mm (GF1521 gold fiducial marker; IZI Medical, Owings Mills, MD, USA). The accuracy of fiducial placement was scored by the interventional radiologist and the radiation oncologist independently based on the fiducial placement accuracy scoring system looking into parameters like inter-fiducial distance, inter-fiducial angle, distance from the centre of the tumor and any gross displacement or complications (Table 1). Score is done by number of fiducials, minimum and maximum distance between fiducials, close to bony structure and any unexpected events. Score of 14–15 is considered very good, 11–13 is good, 8–10 is fair, and 6–7 is poor.

Post procedure pain scoring was done using visual analog pain scale and any complications during or after procedure was recorded. Complications for fiducial placement was scored as per the Society of Interventional Radiology (SIR) grading system [13]. Pain score was done as per Wong-Baker pain scale [14]. Migration of fiducial after placement and during treatment were analyzed and presented in a separate manuscript. The present manuscript is fo-

Table 1. Fiducial placement accuracy scoring and grading system

Parameter	Score		
	1	2	3
No of fiducials placed	1	2	3
Minimum inter-fiducial distance (cm)	< 2	2–4	> 4
Maximum distance from tumor (cm)	> 5	2–5	< 2
Minimum inter-fiducial angle (°)	< 15	> 15	-
Close to metallic objects/bony structure	Yes	No	-
Unexpected events	Yes	No	-

Scores of 14–15 (very good), 11–13 (good), 8–10 (fair), and 6–7 (poor).

https://doi.org/10.3857/roj.2020.00472

Table 2. Demographic profile of HCC patients underwent fiducial placement (n = 108)

Parameter	Value
Gender	
Male	33 (92)
Female	3 (8)
Age (yr)	60.2 (32–76)
ECOG performance status	
0	19 (53)
1	14 (39)
2	3 (8)
Child-Pugh class	
A	32 (89)
B	3 (8)
C	1 (3)
Major liver segment	
II	10 (28)
III	1 (3)
IV	8 (22)
V	5 (14)
VI	8 (22)
VII	2 (6)
VIII	2 (6)
Liver involved	
Only parenchyma	13 (36)
PVT	23 (64)
Dose delivered (Gy)	
23–35	12
36–42	12
45–50	10
Number of fractions	
3	6 (17)
4	1 (13)
5	35 (94)
Post-fiducial	
Treated with CyberKnife	33 (92)
NOT treated	3 (8)

Values are presented as number (%) or mean (range).
HCC, hepatocellular carcinoma; PVT, portal vein thrombosis.

cused on clinical parameters and scoring of fiducial placement.

2. Treatment planning and delivery

Contouring and treatment planning was done on Accuray MultiPlan version 5.3.0 (Accuray Inc., Sunnyvale, CA, USA). Treatment was started on day 4 post-fiducial placement and it was delivered through CyberKnife (M6 model, Accuray Inc.) [15,16]. Details of migration after placement and during treatment were analyzed. CT scan images were taken on day 0 (fiducial placement day), day 3 (CT simulation day) and at end of treatment (day 8). Analysis for fiducial migration was analyzed and will be presented in details in subsequent manuscript.

All the data was collected and analyzed with IBM SPSS version 22 (IBM, Armonk, NY, USA). Association between two categorical variables were assessed by cross tabulation and comparison of percentages. Chi-square test/Fisher exact test was used to test statistical significance. The p-value less than 0.05 was considered statistically significant.

Results

1. Demographic data

One hundred eight fiducials were placed in 36 patients—male, 92%, mean age, 60.2 years; Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, 92%; Child-Pugh A 89%, B&C 11%; majority in segments II and VI; PVT disease 64%—with HCCs (Table 3). Five patients (14%) had lesions in segment V, 8 patients (22%) had in segment VI, and 2 (6%) each in segments VII and VIII. Thirty-three patients (92%) had good performance status (PS 0–1). Only 3 patients (8%) had PS 2, but with small volume disease. Child-Pugh A, B, and C were 32 (89%), 3 (8%), and 1 (3%) patient, respectively. Twenty-nine patients (80%) were treated in five fractions, where as 16% and 4% in 3 and 4 fractions, respectively.

2. Fiducial placement related parameters

Fiducial placement under CT scan and ultrasound-guided were in 25 (69%) and 4 (19%) patients, respectively (Table 3). Time for placement was less than 20 minutes, between 21 and 45 minutes, and more than 45 minutes were in 20 (55%), 13 (36%), and 3 (8%) patients, respectively. All the patients had three fiducials placed under guidance. Post-fiducial severe pain score of 3–4 was only in 2 patients (6%). Majority of the patients had minimal pain (pain score 0–1, 26 patients, 72%) at 1-hour evaluation after placement. Recovery time after fiducial placement was usually less than 20 minutes in majority of the patients (29 patients, 80%). Only 5 patients (14%) had to be under supervision at day care and among them 1 patient (3%) required admission for hemothorax. Five patients (15%) had minor complications requiring intravenous medications (analgesics) (Fig. 1). Among the 5 patients who required admission in day care, 3 patients (9%) had pain abdomen and 2 patients (5%) had pneumothorax. One patient with pneumothorax recovered with supportive medication (oxygen), and 1 patient developed hemothorax and was transferred to intensive care. Three patients (8%) had major displacement (outside liver) immediately after the procedure: one in intestine (abdomen) and two in lung. Majority of the patients (92%) had no displacement after placement.

Table 3. Fiducial placement related parameters (n = 108)

Parameter	Value
Imaging for fiducial placement	
CT scan	25 (69)
CT + ultrasound	4 (11)
Ultrasound alone	7 (19)
Fiducial placement time (min)	
9–20	20 (55)
21–45	13 (36)
> 45	3 (8)
Number of fiducials	
3	36 (100)
1-hour post-fiducial pain score	
0	18 (50)
1	8 (22)
2	8 (22)
3	1 (3)
4	1 (3)
Recovery time (min)	
10–20	29 (80)
20–60	5 (14)
> 60	2 (6)
Grade of recovery	
Poor	1 (3)
Good	2 (6)
Very good	33 (92)
Gross displacement	
No	33 (92)
Yes	3 (8)
Lung	2 (5)
Abdomen	1 (3)
Complications	
No/minimal	30 (83)
Major	1 (3)
Minor	5 (15)
Pain abdomen	3 (9)
Mild pneumothorax	2 (6)
Adverse events requiring admission	
Day care	5 (14)
Indoor admission	1 (3)

Values are presented as number (%).
CT, computed tomography.

3. Evaluation of quality of fiducial placement

Among 108 fiducials placed, majority (24 patients, 67%) of the patients had fiducial placement score of 11–13 (good) (Table 4). Only 3 patients (8%) had poor (score 7) placement score, mostly due to post-fiducial sequel. Four patients (11%) had fair score (score 9–10) and 1 patient had very good score (score 14). Radiologist score of good was in 27 patients (75%), fair in 5 (14%) and poor in 2 (6%) patient, respectively. Radiation oncologist score was good in 26 (72%), fair in 7 (19%) and poor in 3 (8%) patients, respectively. Mean inter-fiducial distance range was 4.7 to 2.5 cm, inter-fiducial angle range was 82.7° to 28.5°, and distance from centre range was 2.1 to 5.1 cm, respectively. Concordance between radiologist score and radiation oncologist score was high (Table 5). Score of "poor" concordance was 2/2 (100%), "fair" score 4/5 (80%) and "good" score 24/27 (89%), respectively ($p = 0.001$).

4. Factors influencing fiducial placement related parameters

Factors influencing fiducial placement related parameters are described in Table 6. Patients with poorer Child-Pugh score ($p = 0.080$), poorer performance status ($p = 0.014$) and patients accrued during the "learning curve" ($p = 0.013$) had poor fiducial placement score. Recovery time was longer in patients with poor Child-Pugh score ($p = 0.025$). Mean placement time was longer in patients with poor performance status ($p = 0.055$). Major complications were higher in patients with poor performance status ($p = 0.009$) and poor Child-Pugh score ($p = 0.034$). Segment of liver involved ($p = 0.484$) and the Barcelona Clinic Liver Cancer (BCLC) stage did not influence fiducial placement score.

5. Learning curve for fiducial placement

There was significant difference in fiducial placement related parameters in first and last 10 patients accrued (Table 7). Good fiducial placement score was only in 30% in first cohort whereas 93% in last cohort ($p = 0.023$). Time for fiducial placement was 42.2 and 14.3 minutes, respectively ($p = 0.069$) in both the cohorts. Recovery time and complications also reduced with the learning curve. Learning curve in fiducial placement may also be due to accrual of relatively advanced patients during the early period of the study.

Discussion and Conclusion

Major bottle-neck for radiosurgery in liver tumour is fiducial placement [17]. There are apprehensions about "seeding" after implant as occurs in gallbladder cancer [8]. Complications such as pain, pneumothorax, migration, de-compensation of liver are major limitations of fiducial placement [5,6,18]. Complications are related to the patient condition and disease status [19,20]. More extensive diseases have higher probability of complications. Apprehensions about the procedure, patient counselling and support system also may influence the compliance and toxicity. Unfortunately, there are only a few published prospective studies evaluating the toxicity after fiducial placement, compliance and assessing the factors influencing the "quality" of fiducial placement [21,22]. The present prospective study has evaluated the quality of fiducial placement, fac-

https://doi.org/10.3857/roj.2020.00472

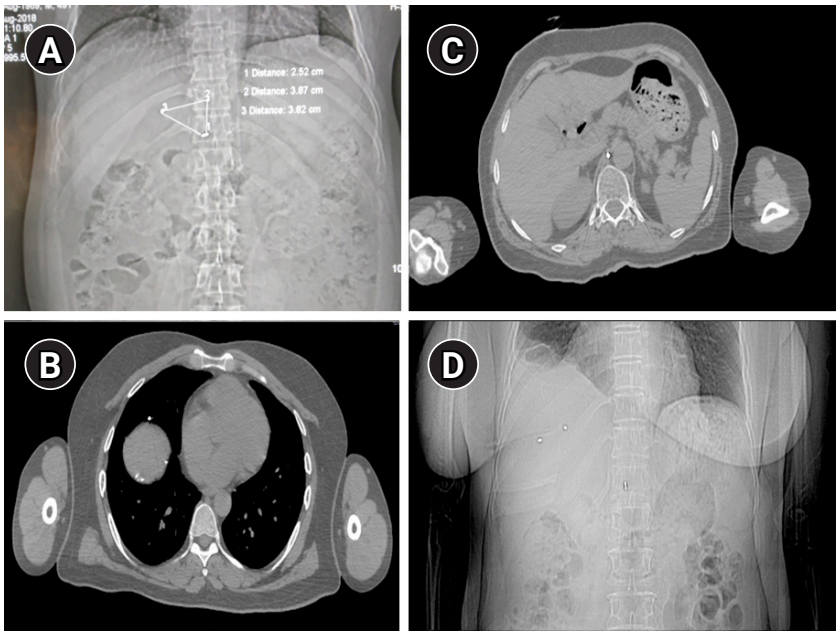


Fig. 1. (A) Ideal placement of fiducial (X-ray anteroposterior topogram). (B) Fiducial migration to lung immediately after placement. (C, D) Fiducial migration to abdomen in computed tomography scan and X-ray anteroposterior topogram.

Table 4. Evaluation the quality of fiducial placement (n = 108)

Parameter	Value
Fiducial placement score	
7	3 (8)
9	1 (3)
10	3 (8)
11	4 (11)
12	7 (19)
13	13 (36)
14	1 (3)
Radiologist score	
Poor	2 (6)
Fair	5 (14)
Good	27 (75)
Very good	2 (5)
Radiation oncologist score	
Poor	3 (8)
Fair	7 (19)
Good	26 (72)
Inter-fiducial distance (cm)	
Max	4.7
Min	2.5
Inter-fiducial angle (°)	
Max	82.7
Min	28.5
Distance from center (cm)	
Max	5.1
Min	2.1

Values are presented as number (%).

tors influencing the quality of placement and also complications after placement. The present study also provides critical information regarding the complication rate in Indian patient population with extensive liver involvement and have relatively poor performance status.

In our study, the interventional radiologist termed 75% of placement as good with regards to accuracy compared to 72% by radiation oncologist. There was a good level of agreement between the radiation oncologist and interventional radiologist on the accuracy of fiducial placement. Segment of liver involved (segment VIII fiducial placement expected to have poorer fiducial placement score) did not show any significant difference. BCLC staging did not show any significant influence in fiducial placement. Patients with extensive liver involvement had poor fiducial placement score. Patient performance status and poorer Child-Pugh score patients had longer recovery time, longer fiducial placement time and higher probability of complications. Hence, the inclusion for fiducial placement and treatment is different. Patients with good performance status, less extensive disease with better Child-Pugh score are ideal candidate for fiducial placement with minimal complications. Better BCLC stage, better Child-Pugh score and small volume disease patients are ideal for radiosurgery treatment. Hence, patients with good performance status, preserved liver function, small volume disease and better Child-Pugh score are ideal candidate for radiosurgery treatment with fiducial placement. The proportion of people with successful fiducial placement in the liver was 92% in our

Table 5. Concordance between radiologist score and radiation oncologist score (n = 36)

Radiologist score	Radiation oncologist score					Concordance (%)
	Poor	Fair	Good	Very good	Total	
Poor	2	0	0	0	2	2/2 (100)
Fair	1	4	0	0	5	4/5 (80)
Good	0	3	24	0	27	24/27 (89)
Very good	0	0	2	0	2	0/2 (0)
Total	3	7	26	0	36	-

study. Out of 3 patient (8%) who had gross fiducial displacement on the day of the procedure, two fiducials (5%) migrated into the lung and one fiducial (3%) migrated into the abdomen. There were no gross migrations seen during treatment or in immediate post treatment period. Post-fiducial placement 83% of patients had no complications. One patient (3%) had major complication in the form of liver decompensation resulting in death. Only 14% of patients had minor complications. Minor complications reported were pain, mild pneumothorax or fatigue post procedure requiring only symptomatic treatment. None of the patients had any complications during or post-treatment. The amount of pain reported post-fiducial placement was very minimal in the study, with the average pain score being 0.86. In literature, pain is the most common complication on any percutaneous procedure. Up to 84% of patients will have at least mild discomfort. When present, pain can usually be managed with short duration of analgesics or narcotics. Bleeding is the most important complication of liver puncture and can be severe when it occurs intraperitoneally [6,7].

Pneumothorax is a rare but serious complication after fiducial placement [5]. Tumour seeding risk is reported around 2.3% in biopsy group and 1% in radiofrequency ablation (RFA) group [8]. Fiducial migrations are uncommon but have implication in treatment delivery [23]. In our study, only 1 patient (3%) had severe adverse effect (death) due to hemothorax. Three patient (9%) had abdominal pain requiring intravenous medication and 2 patients had mild pneumothorax that was resolved with oxygen therapy. Only 5 patients (14%) required admission in day care for more than 1 hour, mostly for pain and pneumothorax management. The complication rates are similar to the published literature. The adverse effects were significantly higher in first ten patients, at the 'learning curve' period and had reduced after placement of adequate number of fiducials. This suggests, high volume centre with adequate exposure will have lesser complications. On the other hand, more advanced cases were accrued during the "learning phase", and hence may have influenced higher morbidity during this period (case selection bias).

Park et al. [2] retrospectively reviewed 101 patients with ultrasound-guided intrahepatic fiducial placement. There were no major complications, although 12 patients (12%) developed minor complications. Technical success was achieved in 291 (97%) fiducial placement. Of 101 patients, 72 patients (71%) fiducials placement was ideal. Marsico et al. [5] assessed how different types of markers affects the tracking accuracy of CyberKnife. Ohta et al. [9] reported success rate of 100% (18/18) for fiducial placement in liver tumours. Only one patient (6%) had mild pneumothorax. There was no gross migration after placement. Oldrini et al. [21] evaluated the imaging technique for fiducial placement and concluded that ultrasound-guided placement is equivalent to CT guided placement. Rong et al. [24] evaluated the migration parameters after placement. Choi et al. [25] evaluated the safety and technical feasibility of endoscopic ultrasonography (EUS)-guided fiducial placement. Of 32 patients, 23 patients (91%) had successful placement and only 1 patient (3%) developed mild pancreatitis which subsided with supportive care. Kim et al. [3] evaluated the safety and technical success rate of an ultrasound-guided fiducial marker implantation. Twenty-one percent had minor complications. Abdominal pain was the most common complication (14%). Fiducial migration occurred in 5 patients (6.5%). Seppenwoolde et al. [22] in their study assessed the accuracy of day-to-day predictions of liver tumour position using implanted gold markers as surrogates and to compare the method with alternative set-up strategies (vertebrae and three-dimensional diaphragm-based set-up). Marker-guidance was superior to guiding treatment using other surrogates. Our study objectives were similar to that of Park et al. [2], Ohta et al. [9], and Choi et al. [25]. Mean age of our study population was 60 years and 92% were male. Similarly, Park et al. [2] reported mean age of 61 years and 73% were male in their study. Child-Pugh score was also similar in both the cohort (Child-Pugh A of 82% in our cohort and 89% in the study of Park et al. [2]). Liver segment involvement was also similar between the two cohort. In our study, all patients (n = 36) had three fiducials implanted. In the study of Park et al. [2], 97 (96%) out of 101 patients had three fiducials. Mean duration of fiducial placement was 23.8 minutes in our study. Time for fiducial placement, "quality" of placement and recovery time was not evaluated in any other study. In our study, mean maximum distance from the tumor center was 5.09, while minimum was 2.09

https://doi.org/10.3857/roj.2020.00472

https://doi.org/10.3857/roj.2020.00472

Table 6. Factors influencing the fiducial related parameters

	Good RO score	p-value	Good R score	p-value	Mean recovery time (min)	p-value	Mean placement time (min)	p-value	Pain score[a]	p-value	Major complication	p-value
Seg of liver		0.484		0.186		0.103		0.304		0.690		0.490
VII–VIII	83		83		16.5		21		0		0	
Other seg	16		79		23.5		25		8		12	
Child-Pugh score		0.080		0.029		0.025		0.156		0.024		0.034
A	78		87		21.5		22.4		6		6	
B&C	25		25		15.5		35.5		75		25	
Age (yr)		0.771		0.545		0.478		0.322		0.623		0.258
< 60	70		76		23.5		22.8		23		6	
> 60	74		84		18.5		24.7		31		10	
ECOG PS		0.014		0.003		0.716		0.055		0.016		0.009
0–1	79		88		21.4		22.3		24		6	
2–3	0		0		14		40.7		67		3	
Involvement		0.433		0.104		0.305		0.478		0.393		0.563
PVT	78		91		22		23.8		22		4	
Parenchyma	62		62		19		23.8		38		2	
Patient accrued		0.013		0.193		0.689		0.094		0.152		0.115
Acc no#1–10	40		60		17		40.6		20		10	
Acc no#11–36	85		88		22.3		17.8		85		7	

Values are in percentages.
RO, radiation oncologist; R, radiologist; ECOG PS, Eastern Cooperative Oncology Group performance status; PVT, portal vein thrombosis.
[a]Grade 3/4.
p-values were derived by the log-rank test.

Table 7. Patient and fiducial placement related parameters in different patient cohort

	Good R score (%)	p-value	Good RT score (%)	p-value	Pain score	p-value	Placement duration	p-value	Recovery time (min)	p-value	Major complication (%)	p-value
Patient no#1–10	50	0.320	30	0.023	20	0.307	42.2	0.069	17.6	0.743	10	0.294
Patient no#11–20	90		90		0		23.5		30.1		10	
Patient no#20–36	97		93		0		14.3		17.1		5	

RO, radiation oncologist; R, radiologist.
p-values were derived by the Pearson chi-square test.

cm. Mean distance between marker and lesion in Park et al. [2] and Oldrini et al. [21] was 3.1 and 3.2 cm, respectively. Maximum and minimum mean inter-fiducial distance in our study was 4.77 and 2.54 cm, respectively. In the study of Oldrini et al. [21], mean distance between the markers was only 1.7 cm. Mean inter-fiducial angle was 82.7° (range, 12° to 117.5°) in our cohort. Successful fiducial placement was 33/36 (92%) in our cohort, whereas in the study of Park et al. [2], it was 97%. Migration immediately after placement was also similar in both the cohort (3% and 2.7%). In our cohort, no complications were seen in 83% and major complication in 1 patient (3%). Park et al. [2] also reported one (2.7%) had major complications and minor complication in 12%. In our cohort, two more patients (5.5%) had decompensation prior to start of treatment and hence treatment was withheld. Fourteen percent of patients had minor complications in the form of either pain, mild pneumothorax or fatigue post procedure which required symptomatic treatment only. Average pain score being 0.86 in our study. Pain scoring was not evaluated in the studies of Park et al. [2] and Choi et al. [25]. In our study, the interventional radiologist termed 75% of placement as good with regards to accuracy compared to 72% by radiation oncologist. There was a good level of agreement between the radiation oncologist and interventional radiologist on the accuracy of fiducial placement. The result in our prospective cohort was similar with the published literature from retrospective series.

The present study is unique in many ways. Strength of the study is that it is a prospective study with accrual of all consecutive liver patients had 108 fiducial placement and were treated with robotic radiosurgery. The self-devised fiducial placement scoring system, pain score and other parameters documented prospectively in all consecutive patients. The present study is one of the only few prospective studies evaluating the fiducial placement score and complications after fiducial placement in liver tumours. Major limitations of the study are relatively smaller sample size (108 fiducials). Scoring systems used for fiducial placement accuracy scoring, recovery grade, and fiducial migration were influenced by the Accuray fiducial system and SIR scoring system for complications, and may need an independent validation.

In summary, fiducial placement is safe and in experienced hands, "quality" of placement is "good" in majority. Major complications and admission after fiducial placement are rare. Complications, fiducial placement time, and recovery time are more during the "learning curve". Patients with poor Child-Pugh score, extensive liver involvement, poor performance status have higher probability of complications. Segment of liver involvement and BCLC stage don't influence fiducial placement "quality". There is a case selection criteria for fiducial placement which is different from patient selection criteria for SBRT treatment.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

We acknowledge Department of Surgical Gastroenterology and Medical Oncology, Amrita Institute of Medical Science, Kochi for the support.

References

1. Balogh J, Victor D 3rd, Asham EH, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma 2016;3:41-53.
2. Park SH, Won HJ, Kim SY, et al. Efficacy and safety of ultrasound-guided implantation of fiducial markers in the liver for stereotactic body radiation therapy. PLoS One 2017;12:e0179676.
3. Kim JH, Hong SS, Kim JH, et al. Safety and efficacy of ultrasound-guided fiducial marker implantation for CyberKnife radiation therapy. Korean J Radiol 2012;13:307-13.
4. Kothary N, Dieterich S, Louie JD, Chang DT, Hofmann LV, Sze DY. Percutaneous implantation of fiducial markers for imaging-guided radiation therapy. AJR Am J Roentgenol 2009;192:1090-6.
5. Marsico M, Gabbani T, Lunardi S, Galli A, Biagini MR, Annese V. Percutaneous ultrasound-guided fiducial marker placement for liver cancer robotic stereotactic radio-surgery treatment: a comparative analysis of three types of markers and needles. Arab J Gastroenterol 2017;18:83-6.
6. Nair VJ, Szanto J, Vandervoort E, et al. Feasibility, detectability and clinical experience with platinum fiducial seeds for MRI/CT fusion and real-time tumor tracking during CyberKnife stereotactic ablative radiotherapy. J Radiosurg SBRT 2015;3:315-23.
7. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8:877-83.
8. Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007;33:437-47.
9. Ohta K, Shimohira M, Murai T, et al. Percutaneous fiducial marker placement prior to stereotactic body radiotherapy for malignant liver tumors: an initial experience. J Radiat Res 2016;57:174-7.

10. Dutta D, Krishnamoorthy S, Sudahar H, Muthukumaran M, Ramkumar T, Govindraj J. Robotic radiosurgery treatment in liver tumors: early experience from an Indian center. South Asian J Cancer 2018;7:175-82.
11. Chen VJ, Oermann E, Vahdat S, et al. CyberKnife with tumor tracking: an effective treatment for high-risk surgical patients with stage I non-small cell lung cancer. Front Oncol 2012;2:9.
12. CyberKnife equipment specifications [Internet]. Sunnyvale, CA: Accuray Worldwide; 2019 [cited 2020 Oct 31]. Available from: http://www.cyberknifelatin.com/pdf/brochure-tecnico.pdf.
13. Cardella JF, Kundu S, Miller DL, Millward SF, Sacks D; Society of Interventional Radiology. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2009;20(7 Suppl):S189-91.
14. Garra G, Singer AJ, Domingo A, Thode HC Jr. The Wong-Baker pain FACES scale measures pain, not fear. Pediatr Emerg Care 2013;29:17-20.
15. Ding C, Saw CB, Timmerman RD. Cyberknife stereotactic radiosurgery and radiation therapy treatment planning system. Med Dosim 2018;43:129-40.
16. Adler JR Jr, Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL. The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 1997;69(1-4 Pt 2):124-8.
17. Shimohigashi Y, Toya R, Saito T, et al. Tumor motion changes in stereotactic body radiotherapy for liver tumors: an evaluation based on four-dimensional cone-beam computed tomography and fiducial markers. Radiat Oncol 2017;12:61.
18. Sotiropoulou E, Stathochristopoulou I, Stathopoulos K, Verigos K, Salvaras N, Thanos L. CT-guided fiducial placement for cyberknife stereotactic radiosurgery: an initial experience. Cardiovasc Intervent Radiol 2010;33:586-9.
19. McGinn CJ, Ten Haken RK, Ensminger WD, Walker S, Wang S, Lawrence TS. Treatment of intrahepatic cancers with radiation doses based on a normal tissue complication probability model. J Clin Oncol 1998;16:2246-52.
20. Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. Semin Radiat Oncol 2001;11:240-6.
21. Oldrini G, Taste-George H, Renard-Oldrini S, et al. Implantation of fiducial markers in the liver for stereotactic body radiation therapy: Feasibility and results. Diagn Interv Imaging 2015;96:589-92.
22. Seppenwoolde Y, Wunderink W, Wunderink-van Veen SR, Storchi P, Mendez Romero A, Heijmen BJ. Treatment precision of image-guided liver SBRT using implanted fiducial markers depends on marker-tumour distance. Phys Med Biol 2011;56:5445-68.
23. Beddar AS, Kainz K, Briere TM, et al. Correlation between internal fiducial tumor motion and external marker motion for liver tumors imaged with 4D-CT. Int J Radiat Oncol Biol Phys 2007;67:630-8.
24. Rong Y, Bazan JG, Sekhon A, Haglund K, Xu-Welliver M, Williams T. Minimal inter-fractional fiducial migration during image-guided lung stereotactic body radiotherapy using Superlock nitinol coil fiducial markers. PLoS One 2015;10:e0131945.
25. Choi JH, Seo DW, Park DH, Lee SK, Kim MH. Fiducial placement for stereotactic body radiation therapy under only endoscopic ultrasonography guidance in pancreatic and hepatic malignancy: practical feasibility and safety. Gut Liver 2014;8:88-93.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):262-269
https://doi.org/10.3857/roj.2020.00626

Real world clinical outcomes of adjuvant sequential chemoradiation in patients with gallbladder carcinomas with poor performance status

Rakesh Kapoor[1,2], Kannan Periasamy[2], Rajesh Gupta[3], Arun Yadav[2], Divya Khosla[2]

[1]*Department of Radiotherapy, Homi Bhabha Cancer Hospital and Research Center, Mullanpur & Sangrur, India*
[2]*Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*
[3]*Department of Surgical Gastroenterology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India*

Received: August 30, 2020
Revised: December 10, 2020
Accepted: December 14, 2020

Correspondence:
Kannan Periasamy
Department of Radiotherapy and Oncology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India
Tel: +91-9442395508
E-mail: pkannan10011988@gmail.com
ORCID
https://orcid.org/0000-0001-7440-0996

Purpose: The purpose of the study is to analyze the overall survival, relapse-free survival, and relapse patterns of adjuvant sequential chemoradiation for gallbladder cancers after curative resection in patients with poor performance status.

Materials and Methods: We retrospectively reviewed clinical records of gallbladder patients with pathologic stage T2-4 or node positivity treated with sequential chemoradiation at our institute between January 2015 and January 2019. Sequential chemoradiotherapy protocol consisted of six cycles of gemcitabine 1,000 mg/m^2 and oxaliplatin 100 mg/m^2 administered every 2 weekly and postoperative radiation therapy (45 Gy in 25 fractions over 5 weeks) by three-dimensional conformal technique.

Results: A total of 36 patients were included. The median overall survival and relapse-free survival was 26 months (95% confidence interval [CI], 21.4–30.5) and 21 months (95% CI, 11.8–30.1), respectively. The 2-year overall and relapse-free survival rates were 55.1% (95% CI, 37.9%–72.3%) and 44.7% (95% CI, 27.5%–61.9%), respectively. Locoregional, systemic, and combined recurrence were noted in 2 (5.5%), 14 (38.8%), and 3 (8.3%) patients, respectively. On univariate analysis, tumour grading significantly influenced relapse free survival; nodal stage and overall stage demonstrated a statistically significant influence on overall survival ($p < 0.05$) with a trend towards significance for lymphovascular invasion. On multivariate analysis, no significant factors were found. Grade 3 and 4 haematological adverse events were observed only in 2 (5.5%) with chemotherapy. No grade 3 and 4 adverse events were observed due to radiation therapy.

Conclusion: Sequential chemoradiation is feasible and tolerable with acceptable efficacy in the adjuvant setting in patients unfit for concurrent chemoradiotherapy.

Keywords: Gallbladder neoplasms, Cholecystectomy, Chemoradiotherapy, Three-dimensional conformal radiotherapy, Survival, Recurrence

Introduction

Biliary tract cancers constitute a heterogeneous group of neoplasms arising from the epithelium of bile ducts. They are classified into cancers of the gallbladder and cholangiocarcinomas, which can be either intrahepatic or extrahepatic [1]. Cancers of the gallbladder account for bulk of biliary tract neoplasms. In India, according to the GLOBOCAN 2018, approximately 25,999 new cases of gallbladder cancer are diagnosed every year and gallbladder cancer ranks 13th among cancer-related mortality. India contrib-

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

utes to approximately 12% of the global burden of gallbladder cancer [2-4]. Surgery is the definitive treatment for cure for localized resectable cancers which account for approximately 10%–20% of tumours [5-7]. After curative resection alone, the recurrence remains high with the literature review suggesting a locoregional recurrence rate of 30%–65% and distant recurrence as high as 80% [8,9]. These findings reveal that relapses, both locoregional and distant, are common after curative resection, rationalizing the consideration of use of radiation and systemic therapy in the adjuvant setting to reduce the relapse rates and thereby improve the survival and quality of life. Various treatment options that have been utilized include surveillance, adjuvant chemotherapy, adjuvant radiotherapy with or without concurrent chemotherapy, and adjuvant chemotherapy followed by concurrent chemoradiotherapy [10-16]. Lacking adequate high quality prospective clinical evidence comparing adjuvant treatment modalities due to low number of resected cases, the benefit of adjuvant therapy in these cancers is often unclear amid several therapeutic options. Sequential chemoradiotherapy consisting of chemotherapy and radiotherapy is the adjuvant therapy followed at our institute after curative resection in patients who are not fit enough to tolerate concurrent chemoradiation. In the present study, we retrospectively analyzed the outcomes of those gallbladder cancers treated with adjuvant sequential chemoradiation.

Materials and Methods

1. Study design and patients

We retrospectively reviewed records of gallbladder cancer patients treated with curative surgery and adjuvant sequential chemoradiation at our institute between January 2015 and January 2019. The flow diagram outlining the selection criteria of the study has been depicted in Fig. 1. Unresectable and metastatic diseases were excluded. Perfectly fit individuals treated with concurrent chemoradiotherapy were also excluded. Sequential chemoradiotherapy is being followed in our institute for patients who are not fit enough to tolerate concurrent chemoradiotherapy—Zubrod performance status 2 or more or with comorbidities. The sequential chemoradiotherapy protocol included 6 cycles of gemcitabine and oxaliplatin and postoperative radiation therapy. Adjuvant therapy was started 4 weeks after surgery. All patients planned for adjuvant sequential chemoradiotherapy were begun treatment with chemotherapy. Radiotherapy was delivered whenever patients obtained their slots in the machine. Eighteen patients received radiation after 2–3 cycles of chemotherapy and 18 patients received radiotherapy after completion of 6 cycles of chemotherapy. A gap of 3–4 weeks was allowed between chemotherapy and radiotherapy. Staging of tumours was done retrospectively with the American Joint Committee on Cancer (AJCC) 8th edition. No study-specific consent form was obtained as it was a retrospective analysis. All patients who underwent treatment had a valid consent form which included permission for use of data and information for research.

2. Chemotherapy protocol

The chemotherapy regimen consisted of gemcitabine 1,000 mg/m^2 and oxaliplatin 100 mg/m^2 administered every 2 weeks for a total of 6 cycles. Blood investigations including complete blood count, renal function tests, and liver function tests were obtained prior to each cycle. Chemotherapy was deferred for a week if total leucocyte count was $<3,000$ cells/mm^3 absolute neutrophil count was $<1,500$ cells/mm^3 or platelet count $<100,000$ cells/mm^3. Dose reduction was considered if patients developed more than 2 delays or grade 3 neutropenia or thrombocytopenia or febrile neutropenia.

3. Radiotherapy protocol

A planning computed tomography (CT) scan with intravenous contrast with a slice thickness of 3 mm was acquired through the region of interest with the patient in a supine position using T-bar. The target volume for postoperative radiotherapy included the tumour bed and regional lymph nodes. The clinical target volume (CTV) tumour bed consists of gallbladder fossa and surgical clips with a 1-cm isotropic expansion. Porta hepatis, coeliac, and para-aortic nodes were contoured as regional lymph nodes. Porta

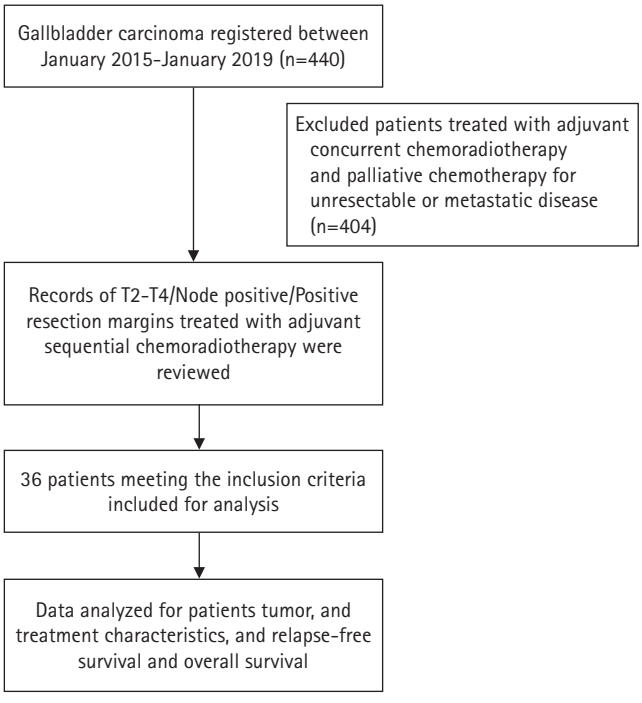


Fig. 1. Flow diagram depicting the selection criteria of the study.

hepatis was delineated from bifurcation of portal vein to superior mesenteric vein or splenic vein with a 1-cm expansion. The coeliac axis encompasses the proximal 1.5 cm of the celiac artery with a 1-cm expansion. The aorta is contoured from the superior most contour of either celiac axis or the portal vein, whichever is more superior up to the lower border of the L2 lumbar vertebra. An asymmetric expansion is then given from the aorta, 3 cm to the right, 1 cm to the left, 2.5 cm to the front, and 0.2 cm to the back to create the para-aortic nodal volume. All the nodal volumes are fused to generate the nodal CTV. A margin of 1–2 cm in the supero-inferior direction and 0.5–1 cm laterally are given from the CTV to generate the planning target volume (PTV) to account for setup and respiration related uncertainties. The organs-at-risk (OARs) that were contoured include liver, bilateral kidneys, and spinal cord. Radiation therapy was planned by three-dimensional conformal radiation therapy technique (3D-CRT) using three fields and delivered to a total dose of 45 Gy in 25 fractions at 1.8 Gy per fraction over 5 weeks. The dose distribution of a patient is shown in Fig. 2.

4. Follow-up

After completing adjuvant treatment, follow-up was done once in 3 months for the first 2 years, then every 6 months for the next 3 years, and then annually. The follow-up evaluation comprised of clinical examination, blood investigations including CA19-9, and imaging with ultrasonography and CT as required.

5. Outcomes assessed

The primary objective of the study was to estimate the overall survival and relapse-free survival with sequential chemoradiation. The secondary objectives were to assess the relapse pattern, toxicity and factors influencing overall survival and relapse-free survival.

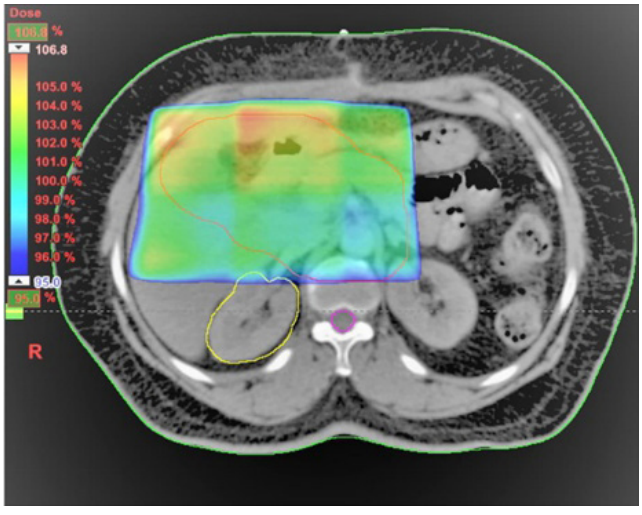


Fig. 2. Dose distribution.

Overall survival and relapse-free survival were calculated from the date of surgery to date of death for any reason or to date of last follow-up and date of relapse, respectively. Relapses were documented as locoregional (recurrence in the tumour bed or regional lymph nodes), distant (recurrence in distant organs or non-regional lymph nodes), or both.

6. Statistical analysis

Categorical data were presented as numbers and percentages. Median and range were used to express the numerical data. Overall survival and relapse-free survival were estimated by Kaplan-Meier survival method with 95% confidence interval (CI). The cut-off date for censoring of patients who were alive was April 2020 and survival status were assessed telephonically if patients were unable to come for follow-up. A univariate analysis using log-rank test and multivariate analysis using Cox proportional hazards model were performed to evaluate the prognostic factors having a significant impact on overall survival. A p-value <0.05 was considered statistically significant.

Results

The study included 36 patients of gallbladder cancers who underwent curative resection and completed adjuvant treatment with sequential chemoradiotherapy. The characteristics of the patients and the disease were summarised in Table 1. The median age was 55.5 years. Approximately two-thirds (61.1%) of the cases were females and one-fourth (25%) had incidentally detected carcinomas diagnosed during surgery for gallstone disease. Extended cholecystectomy alone was performed in 86.1% of patients. Wedge resection of liver, anatomical resection of segments 4b and 5, and right hepatectomy were performed in 26 (72.2%), 6 (16.6%), and 4 (11.1%) patients, respectively. Additional procedures like sleeve duodenectomy, pancreatoduodenectomy, and resection of colon were performed in 5 patients (13.8%). Adenocarcinoma and squamous cell carcinoma histology were present in 88.9% and 8.3% of patients, respectively. Distribution of patients in various grades of tumour differentiation included: well-differentiated (19.4%), moderately differentiated (72.2%), and poorly differentiated tumours (8.3%). The majority of patients were stage IIIA (41.7%) and IIIB (25%). Positive resection margins, lymphovascular space invasion, and perineural invasion were observed in 5 (13.9%), 7 (19.4%), and 13 (36.1%) patients, respectively. Approximately 50% of patients received radiation therapy after completion of chemotherapy.

In general, the treatment was well tolerated and compliance with the protocol was good. A total of 32 patients (88.8%) completed no less than four cycles of planned chemotherapy; 25 pa-

https://doi.org/10.3857/roj.2020.00626

Table 1. Patient and disease characteristics

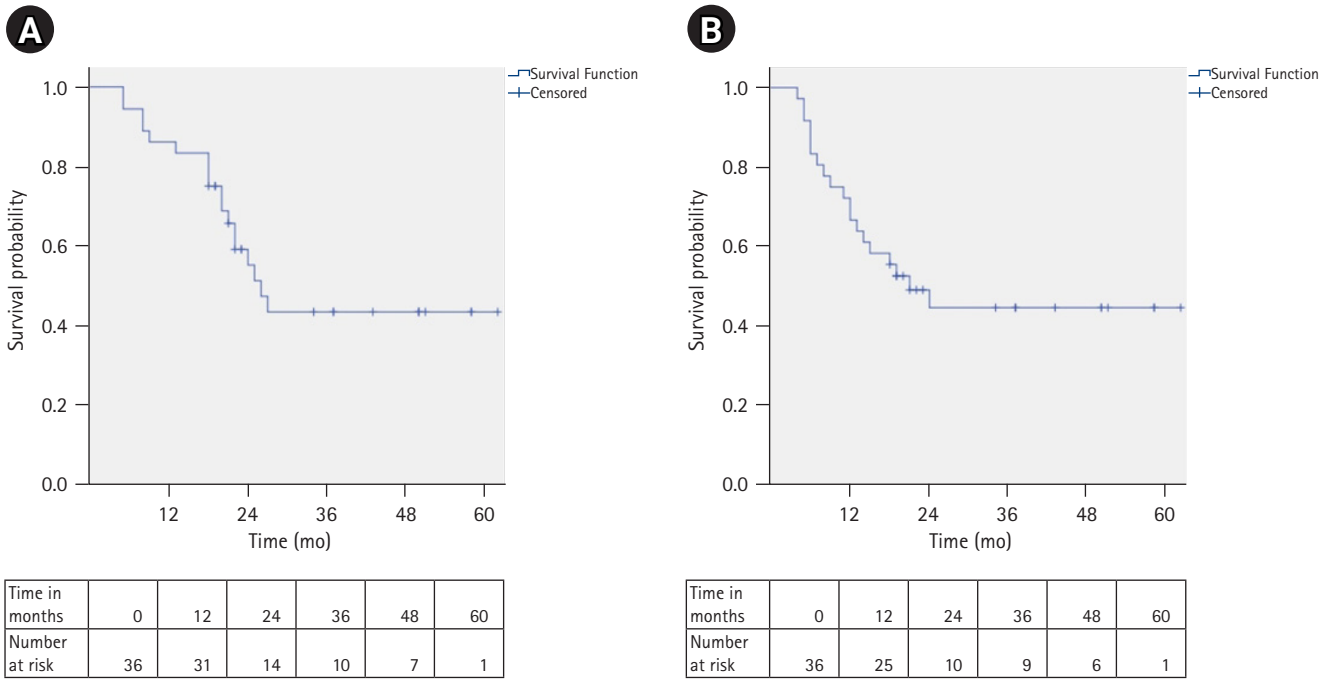
Characteristic	Value
Age (yr)	55.5 (24–76)
Sex	
Male	14 (38.9)
Female	22 (61.1)
Incidental detection	
Yes	9 (25.0)
No	27 (75.0
Type of surgery	
Extended cholecystectomy	
Wedge liver resection	26 (72.2)
Anatomical liver resection	6 (16.6)
Right hepatectomy	4 (11.1)
Additional procedures	
Sleeve duodenectomy	2 (5.5)
Pancreatoduodenectomy	1 (2.7)
Resection of colon	2 (5.5)
Histology	
Adenocarcinoma	32 (88.9)
Adenosquamous	1 (2.8)
Squamous cell carcinoma	3 (8.3)
Differentiation	
Well differentiated	7 (19.4)
Moderately differentiated	26 (72.2)
Poorly differentiated	3 (8.3)
T stage	
T2b	13 (36.1)
T3	23 (63.9)
N stage	
N0	25 (69.4)
N1	10 (27.8)
N2	1 (2.8)
Stage grouping	
IIB	11 (30.6)
IIIA	15 (41.7)
IIIB	9 (25.0)
IVB	1 (2.8)
Resection status	
R0	31 (86.1)
R1	5 (13.9)
Lymphovascular space invasion	
Negative	29 (80.6)
Positive	7 (19.4)
Perineural invasion	
Negative	23 (63.9)
Positive	13 (36.1)

Values are presented as median (range) or number (%).

tients (69.4%) received all six cycles. The causes for cessation of chemotherapy included disease relapse in 5, haematological toxicity in 2, and unknown reasons in 4. Sixteen patients (34.7%) had haematological toxicity. Grades 1, 2, and 3 leucopoenia were observed in 4 (11.1), 4 (11.1%), and 1 patient (2.8%), respectively. Grades 1, 2, 3, and 4 thrombocytopenia were present in 3 (8.3%), 2 (5.6%), 1 (2.8%), and 1 (2.8%) patient, respectively. All patients completed the radiation therapy without any unscheduled interruption. The most common toxicities during radiation were grade 1 skin toxicity and grade 1 vomiting. None of the patients developed radiation therapy related grade 3 and grade 4 complications.

The median follow-up was 21 months (range, 5 to 62 months). The median overall survival and relapse-free survival were 26 months (95% CI, 21.4–30.5) and 21 months (95% CI, 11.8–30.1), respectively (Fig. 3A, 3B). The 2-year overall survival was 55.1% (95% CI, 37.9%– 72.3%) and the 2-year relapse-free survival was 44.7% (95% CI, 27.5%–61.9%). Of the 36 patients, recurrences were observed in 19 (52.8%) as shown in Table 2. Fourteen patients (73.6%) had isolated systemic relapses. Both locoregional and distant recurrences were seen in 3 patients (15.7%); 2 patients (10.5%) had isolated locoregional recurrence. Locoregional recurrences were primarily seen as periportal lymph nodes (21%). The most common sites of distant metastases included liver (36.8%) and peritoneum (36.8%). Fig. 4 summarises the various sites of relapses. Of the 19 relapses, 8 (6 distant, 2 combined) occurred in the chemotherapy followed by radiation group and 11 (2 local, 8 distant, 1 combined) in the sandwich radiation group. Eight patients received palliative chemotherapy with capecitabine for relapses, whereas 11 patients were kept under best supportive care in view of poor performance status and disseminated disease. One patient received palliative radiotherapy to a dose of 20 Gy in 5 fractions for the abdominal wall deposit.

A univariate analysis to identify factors influencing relapse free survival and overall survival after radical surgery was carried out. Table 3 summarises the results of the univariate analysis. The findings revealed that nodal status and overall stage grouping, were significantly associated with overall survival ($p < 0.05$). Grading of tumours significantly influenced relapse-free survival ($p = 0.007$). Primary tumour stage and lymphovascular invasion demonstrated a close trend for statistically significant association with overall survival. The comparison of survival curves based on nodal staging is shown in Fig. 5. Further, there was a trend towards better overall survival with female sex. All other parameters like positive resection margin, perineural invasion, poorly differentiated tumours, and sequencing of adjuvant therapy (chemotherapy→radiotherapy→chemotherapy) though associated with poor survival, did not show statistical significance. Table 4 depicts the results of multi-



Time in months	0	12	24	36	48	60
Number at risk	36	31	14	10	7	1

Time in months	0	12	24	36	48	60
Number at risk	36	25	10	9	6	1

Fig. 3. The estimated survival probability: (A) overall survival and (B) relapse-free survival.

Table 2. Distribution and pattern of recurrence

Recurrence	Value
No recurrence	17 (47.2)
Locoregional	2 (5.5)
Distant	14 (38.8)
Locoregional + distant	3 (8.3)

Values are presented as number (%).

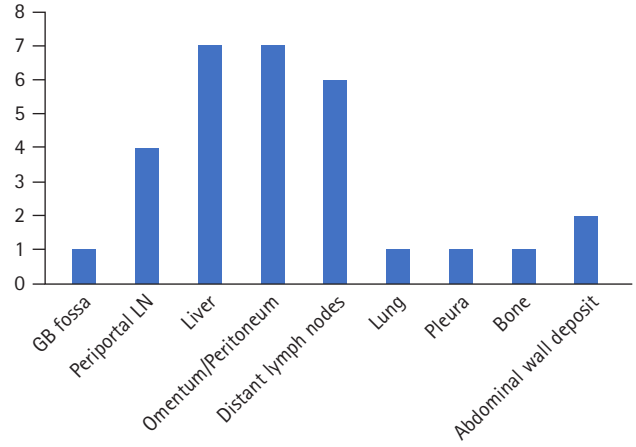


Fig. 4. Sites of relapse. GB, gallbladder; LN, lymph node.

variate analysis for survival performed using Cox proportional hazards model. None of the adverse features including grading, resection status, lymphovascular and perineural invasion have been found to be significantly associated with relapse-free survival and overall survival with sequential chemoradiotherapy.

Discussion and Conclusion

Carcinomas of gallbladder constitute majority of biliary tract neoplasms and it is more common in females than males [1-4]. In our study, nearly two-thirds of cases were females. As most of these patients often present with either unresectable or metastatic disease, the prognosis is dismal. Among patients who underwent curative resection, the outcomes are often poor owing to locoregional and distant recurrence, justifying the need for adjuvant therapy. Though several adjuvant treatments have been tried, yet a standard consensus adjuvant approach has not been reached, mainly due to lack of robust prospective evidence [10-16]. Though studies utilizing concurrent chemoradiotherapy with either 5-fluorouracil or gemcitabine [11,13,14] are largely available, as such, studies addressing sequential chemoradiation are very limited.

The results of our study suggest that sequential chemoradiation may be effective and better tolerated in patients requiring adjuvant treatment after curative resection and not fit enough to tolerate concurrent chemoradiotherapy. Wang et al. [17] reported a median survival of 8 months (95% CI, 8–9) with observation in patients with T2 and node positive disease postsurgical resection. However, with adjuvant radiotherapy, authors reported median survival of 15 months (95% CI, 13–16) and the 2-year overall survival as 30%. A

https://doi.org/10.3857/roj.2020.00626

Table 3. Univariate analysis of RFS and OS using log-rank test

Factor	2-yr RFS (%)	Median RFS (mo)	p-value	2-yr OS (%)	Median OS (mo)	p-value
Sex						
Male	40	15	0.493	25.7	20	0.087
Female	48.1	NR		53.7	NR	
Age (yr)						
≤ 60	41.7	19	0.518	40	24	0.584
> 60	50.9	NR		48.5	26	
Grade						
Well/moderately differentiated	48.7	24	0.007	45	26	0.183
Poorly differentiated	0	8		33.3	18	
T stage						
T2b	57.7	NR	0.170	64.5	NR	0.099
T3	37.3	15		31.1	22	
N stage						
N0	47	21	0.202	47.8	27	0.025
N1	40	24		35	26	
N2	0	7		0	8	
Stage						
IIB	63.6	NR	0.219	71.6	NR	0.019
IIIA	37.3	15		33.9	24	
IIIB	27.8	24		22.2	25	
IVB	0	7		0	8	
Resection status						
R0	45.7	24	0.449	44.8	26	0.180
R1	40	14		40	18	
Lymphovascular space invasion						
Negative	54.2	14	0.077	50.1	NR	0.062
Positive	0	21		0	20	
Perineural invasion						
Negative	54.1	18	0.320	47.8	NR	0.994
Positive	28.8	21		33.8	26	
Sequence of treatment						
Chemotherapy followed by radiotherapy	50	24	0.259	44.6	27	0.570
Chemotherapy→radiotherapy→chemotherapy	38.9	15		41.3	22	

RFS, relapse-free survival; OS, overall survival; NR, not reached.

retrospective study on analysis of efficacy of postoperative adjuvant radiotherapy on 127 gallbladder patients by Yang et al. [12] reported a median survival of 16.9 months for stage III patients. Studies with concurrent chemoradiotherapy with fluorouracil showed a median survival of 1.9 years [11]. Results of the present study with sequential chemoradiation show a median survival of 26 months (95% CI, 21.4–30.5) and 2-year survival of 55.1% (95% CI, 37.9%–72.3%) which may be non-inferior to concurrent chemoradiotherapy. A median survival of 35 months and 2-year survival rate of 65% (95% CI, 53%–74%) was reported in the SWOG trial in which cases of cholangiocarcinomas and gallbladder carcinomas were clubbed and received adjuvant chemotherapy followed by capecitabine based concurrent chemoradiotherapy. Results of our study have lower median survival when compared to adjuvant chemotherapy followed by concurrent chemoradiotherapy, which could be attributed to the lack of concurrent chemotherapy with radiation. However, it must be remembered that in SWOG trial, approximately 52% of patients experienced grade 3 and 11% experienced 4 adverse events. The most frequently encountered toxicities were neutropenia, hand-foot syndrome, diarrhoea, and lymphopenia [15] whereas in the present study of sequential chemoradiation, only two cases experienced grades 3 and 4 haematological side effects. This suggests that sequential chemo radiation may be an effective suitable option in patients who are not

fit enough to tolerate concurrent chemotherapy.

When we look at the recurrence rates, the published retrospective studies of radiotherapy or chemoradiotherapy in the adjuvant setting have shown a recurrence rate of 39% to 69% in the locoregional area and systemic recurrence as high as 80% whereas our data with sequential chemoradiation exhibited a locoregional recurrence rate of 26.3% and systemic relapse rate of 38.8%, similar to that reported in SWOG trial in which concurrent capecitabine based chemoradiotherapy was used [8-16,18]. Several factors like nodal status, T stage, resection margin, lymphovascular invasion, perineural invasion, and grade have been shown to influence outcome in several series [13,16]. The present study also revealed grading to influence relapse-free survival and node positivity, and overall stage grouping as statistically significant factors influencing overall survival on univariate analysis; there was a trend for statistical significance with primary tumour stage and lymphovascular invasion. However, resection margins in our study did not have a statistically significant impact on survival which may be due to small number of patients with positive margins in our study.

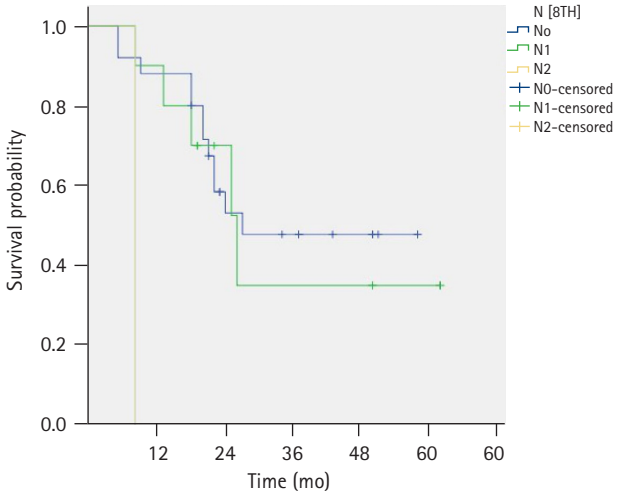


Fig. 5. Comparison of survival curve based on nodal staging.

Recently, there had been three prospective randomized trials that compared adjuvant chemotherapy versus observation [19-21]. The PRODIGE and BCAT trials demonstrated that adjuvant gemcitabine-based chemotherapy alone was not superior to observation in biliary tract cancers. BILCAP trial, the largest randomized trial to date, though did not meet its primary endpoint showed a significant overall survival benefit with adjuvant capecitabine according to per-protocol analysis. However, in that trial, it was observed that the overall survival was considerably higher in the observation arm also (60%).

Based on the BILCAP trial, capecitabine is considered as the new standard after surgery and had been incorporated in the American Society of Clinical Oncology 2019 guideline. However, all these trials do not have radiation therapy in the adjuvant arms, thus, making the contribution of postoperative radiotherapy unclear [22].

In conclusion, the present study has revealed that sequential chemoradiation is a feasible, safe and tolerable regimen with acceptable efficacy in the adjuvant setting in patients with adverse features who are not fit enough to tolerate concurrent chemoradiation. The drawback of our study is retrospective design and no comparative arm. In the present situation where adjuvant capecit-

Table 4. Multivariate analysis of RFS and OS using Cox proportional hazards model

Factor	RFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Grade				
Well/moderately differentiated	1		1	
Poorly differentiated	4.340 (0.681–27.642)	0.120	1.678 (0.246–11.427)	0.597
N stage				
Node negative	1		1	
Node positive	1.107 (0.399–3.075)	0.845	1.278 (0.437–3.738)	0.654
Resection status				
R0	1		1	
R1	1.484 (0.342–6.433)	0.598	2.011 (0.503–8.030)	0.323
Lymphovascular space invasion				
Negative	1		1	
Positive	1.098 (0.221–5.464)	0.909	1.828 (0.399–8.374)	0.437
Perineural invasion				
Negative	1		1	
Positive	1.383 (0.525–3.643)	0.512	0.890 (0.330–2.404)	0.819

RFS, relapse-free survival; OS, overall survival; CI, confidence interval.

https://doi.org/10.3857/roj.2020.00626

abine could be considered as a new standard of care based on the BILCAP trial, the benefit of radiation therapy is unclear. Therefore, prospective randomized controlled trials incorporating adjuvant radiotherapy with chemotherapy are required to confirm the benefit of radiation therapy after curative surgery.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Ahn DH, Bekaii-Saab T. Biliary cancer: intrahepatic cholangiocarcinoma vs. extrahepatic cholangiocarcinoma vs. gallbladder cancers: classification and therapeutic implications. J Gastrointest Oncol 2017;8:293-301.
2. The Global Cancer Observatory. Population fact sheet of India [Internet]. Paris, France: International Agency for Research on Cancer, World Health Organization; 2020 [cited 2020 Dec 15]. Available from: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf.
3. Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. Clin Exp Hepatol 2019;5:93-102.
4. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51:349-64.
5. Boerma EJ. Towards an oncological resection of gall bladder cancer. Eur J Surg Oncol 1994;20:537-44.
6. Matsumoto Y, Fujii H, Aoyama H, Yamamoto M, Sugahara K, Suda K. Surgical treatment of primary carcinoma of the gallbladder based on the histologic analysis of 48 surgical specimens. Am J Surg 1992;163:239-45.
7. Gibby DG, Hanks JB, Wanebo HJ, et al. Bile duct carcinoma: diagnosis and treatment. Ann Surg 1985;202:139-44.
8. Kopelson G, Galdabini J, Warshaw AL, Gunderson LL. Patterns of failure after curative surgery for extra-hepatic biliary tract carcinoma: implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1981;7:413-7.
9. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003;98:1689-700.
10. Bosset JF, Mantion G, Gillet M, et al. Primary carcinoma of the gallbladder: adjuvant postoperative external irradiation. Cancer 1989;64:1843-7.
11. Czito BG, Hurwitz HI, Clough RW, et al. Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience. Int J Radiat Oncol Biol Phys 2005;62:1030-4.
12. Yang L, Feng FL, Zhou HH, Sun YJ, Meng Y. [Analysis of the efficacy of postoperative radiotherapy in gallbladder cancer]. Zhonghua Zhong Liu Za Zhi 2013;35:534-9.
13. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. Int J Radiat Oncol Biol Phys 2009;75:150-5.
14. Kresl JJ, Schild SE, Henning GT, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002;52:167-75.
15. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33:2617-22.
16. Agrawal S, Gupta PK, Rastogi N, et al. Outcomes of adjuvant chemoradiation and predictors of survival after extended cholecystectomy in gall bladder carcinoma: a single institution experience from an endemic region. J Gastrointest Cancer 2015;46:48-53.
17. Wang SJ, Fuller CD, Kim JS, Sittig DF, Thomas CR Jr, Ravdin PM. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. J Clin Oncol 2008;26:2112-7.
18. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012;30:1934-40.
19. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. J Clin Oncol 2019;37:658-67.
20. Ebata T, Hirano S, Konishi M, et al. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. Br J Surg 2018;105:192-202.
21. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663-73.
22. Shroff RT, Kennedy EB, Bachini M, et al. Adjuvant therapy for resected biliary tract cancer: ASCO Clinical Practice Guideline. J Clin Oncol 2019;37:1015-27.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):270-281
https://doi.org/10.3857/roj.2020.00619

Dosimetric comparative study of 3DCRT, IMRT, VMAT, Ecomp, and Hybrid techniques for breast radiation therapy

Semaya Natalia Chen[1,2], Prabhakar Ramachandran[1,3], Pradip Deb[1]

[1]*School of Health and Biomedical Sciences, RMIT University, Melbourne, Australia*
[2]*Department of Radiation Oncology, National Cancer Centre Singapore, Singapore*
[3]*Princess Alexandra Hospital, Queensland, Australia*

Received: August 28, 2020
Revised: October 21, 2020
Accepted: November 9, 2020

Correspondence:
Pradip Deb
Medical Radiations, School of Health and Biomedical Sciences, RMIT University, Victoria, Australia
Tel: +61 3 99257324
E-mail: Pradip.Deb@rmit.edu.au
ORCID:
https://orcid.org/0000-0003-3612-0859

Purpose: To assess and compare the dosimetric parameters obtained between three-dimensional conformal radiotherapy (3DCRT), three-dimensional field-in-field (3DFIF), 5-field intensity-modulated radiotherapy (IMRT MF5), tangential IMRT (tIMRT), tangential volumetric modulated arc therapy (tVMAT), electronic tissue compensation (Ecomp), and Hybrid treatment plans.
Material and Methods: Thirty planning computed tomography datasets obtained from patients previously treated with whole breast radiation therapy (WBRT) were utilized in this study. Treatment plans were created for 3DCRT, 3DFIF, IMRT MF5, tIMRT, tVMAT, Ecomp, and Hybrid techniques using Eclipse Treatment Planning System (version 13.6) with a prescribed dose of 42.5 Gy in 16 fractions.
Results: Techniques with tangential beams produced statistically significantly better organs-at-risk (OARs) dosimetry ($p < 0.001$). Planning target volume Homogeneity Index (HI) was found to be significantly different among all techniques ($p < 0.001$), with Ecomp resulting in better HI (1.061 ± 0.029). Ecomp was also observed to require relatively shorter planning time ($p < 0.001$).
Conclusions: Techniques using tangential fields arrangements produced improved OARs dosimetry. Of all the treatment planning techniques employed in this study, Ecomp was found to be relatively easy to plan and produce acceptable dosimetry for WBRT in a short time.

Keywords: Whole breast radiation therapy, Conformal radiotherapy, Intensity modulated radiotherapy, Electronic tissue compensation

Introduction

Breast cancer refers to cancer originating in the breast tissues, including the ducts and lobules [1]. According to the latest statistics published by the International Agency for Research on Cancer (IARC), breast cancer ranks as the second most commonly diagnosed cancer in the world. It also highlighted breast cancer as the most common cancer in females worldwide and is the first and second leading cause of all cancer-associated deaths in females in developing and developed regions, respectively [2]. Implementation of breast screening programmes have brought forward the lead time for detecting early breast cancer enabling improved treatment outcome [3]. For patients diagnosed with early-stage breast cancer, conservative management approach of breast-conserving surgery (BCS) is preferred over radical mastectomy commonly used in patients with late-stage breast cancer. The 13th St. Gallen International Breast Cancer Conference (2013) Expert Panel [4] however highlighted that unless post-operative radiation therapy could be delivered, BCS should be reconsidered. Addition of radiation therapy would help to reduce recurrence rates by eradicating the likely presence of microscopic disease after surgery [5]. Currently, radiation therapy presents as an integral component of early-stage, localised breast cancer treatment [5,6]. A large meta-analysis [7] found that radiation therapy delivered post-surgery resulted in ap-

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

parent reduction in the risk of local recurrences and mortality rate. In addition to improving the local and regional control, use of radiation therapy post-surgery for early-stage breast cancer treatment, also provided the advantage of maintaining patients' quality of life (QOL) to a certain extent. This was attributed to the ability of keeping their breasts, thus maintaining their body image and femininity [6,8].

Radiation therapy is an integral component of early-stage breast cancer management and typically applied to the whole breast post-BCS [9]. Results obtained from randomized trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [7] revealed that whole breast radiation therapy (WBRT) post-BCS reduced rate of disease recurrence by half and mortality rate by a 6th for patients with early-stage breast cancer. Conventional approach of WBRT is with the use of three-dimensional conformal radiation therapy (3DCRT). However, this approach is associated with the challenge of achieving uniform target dose distribution [10] and introduction of undesired dose to the skin and adjacent organs, resulting in acute and long-term toxicities [6]. These issues stemmed from the steep breast contour change in the 3D shape of the breast and the proximity of target volume to critical organs and tissues. To address these challenges, advanced and complex radiation therapy technology have been developed over the years to increase target dose uniformity, reduce high-dose regions and doses to organs-at-risk (OARs). These are manifested in techniques such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and electronic tissue compensation (Ecomp). However, there are trade-offs involved in these techniques in an attempt to improve the planning target volume (PTV) and OARs dosimetry. It was also documented in literature that several institutions and radiation therapy departments utilize varying treatment techniques and fractionation schedules for breast radiation treatments [11,12]. These differences could result in overall compromised quality of patient care, manpower, available resources and productivity of the department. Additionally, consensus on the optimal technique to be employed for WBRT is still lacking both in literature and clinically. There is also currently limited clinical implementation, research and data available on the use of other advanced techniques like Ecomp and Hybrid for WBRT compared to the other more commonly utilized techniques. Hence, the full extent of their effectiveness on breast cancer treatment remains only partially understood. Therefore, this study aims to: (1) assess the PTV dosimetry and determine the doses delivered to OARs for WBRT using the various treatment planning techniques; (2) evaluate and compare all the dosimetric parameters obtained for both PTV and OARs between the various techniques; and (3) identify an optimal technique that would be recommended for WBRT based on the comparison results.

Materials and Methods

1. Patient selection

This retrospective study utilized thirty anonymized planning computed tomography (CT) datasets of early-stage female breast cancer patients previously treated with WBRT. To maintain diversity of breast sizes and shapes, 13 right-sided and 17 left-sided cases with various breast volumes and separations were selected (Table 1). Every identifiable patient data was replaced with unique numbers as part of de-identification step, according to the centre's ethics protocol.

Planning CT datasets were acquired using Philips CT Big Bore (Philips Healthcare, Best, The Netherlands) with patients lying supine on a lift-up board and arms raised above the head. Each slice of acquired CT datasets was 3 mm in thickness. Image registration and delineation of gross tumour volume (GTV), PTV and OARs were performed using Eclipse Treatment Planning System (TPS) (version 13.6.23; Varian Medical Systems, Palo Alto, CA, USA). GTV and PTV were contoured by the radiation oncologist. Contoured OARs included contralateral breast (CB), heart, liver, left lung, right lung, and total bilateral lungs. Lung volumes were contoured using auto-threshold function of the planning system. Heart volume was contoured based the heart atlas guidelines. Both CB and liver were delineated based on the visible breast and liver tissues, respectively.

2. Treatment planning

As conventional 3DCRT and incorporation of field-in-fields (3DFIF) is still considered to be the standard of care in breast cancer radiation treatment in many institutions, they were also included in this study for dosimetric comparison. For each dataset, 7 distinct plans, namely conventional 3DCRT, 3DFIF, Ecomp, Hybrid, tIMRT, IMRT MF5, and tVMAT were generated and compared against each other. In the case of Hybrid, tIMRT, IMRT MF5, and tVMAT treatment planning techniques, a separate structure encompassing the entire affected breast was contoured and labelled as IMRT PTV for each dataset. All treatment plans were produced in Eclipse TPS at RMIT University. A reference point at isocentre location was used to nor-

Table 1. Range of breast volumes and breast separations (n = 30)

	Mean ± SD	Median (range)
Breast volume (cm^3)	1,127.28 ± 559.54	1,089.78 (433.21–2,573.83)
Breast separation (cm)	21.70 ± 2.72	21.76 (17.08–27.36)

SD, standard deviation.

Table 2. Planning goals for PTV, IL, CL, CB, heart, and liver

Structure	Planning goals
PTV	Minimum dose (PTV_{Dmin}) = 95% dose (40.38 Gy)
	Maximum dose (PTV_{Dmax}) = 107% dose (45.48 Gy)
IL	Percentage volume of IL receiving 5 Gy (IL_{V5Gy}) < 60%
	Percentage volume of IL receiving 20 Gy (IL_{V20Gy}) < 30%
	Percentage volume of IL receiving 30 Gy (IL_{V30Gy}) < 10%
CL	Percentage volume of CL receiving 10 Gy (CL_{V10Gy}) = 0%
CB	Mean CB dose (CB_{Dmean}) < 2.5 Gy
	Percentage volume of CB receiving 5 Gy (CB_{V5Gy}) < 15%
Heart	Mean heart dose ($Heart_{Dmean}$) < 4 Gy
	Percentage volume of heart receiving 5 Gy ($Heart_{V5Gy}$) < 40%
	Percentage volume of heart receiving 20 Gy ($Heart_{V20Gy}$) < 10%
Liver	Mean liver dose ($Liver_{Dmean}$) < 20 Gy

PTV, planning target volume; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast.

malize the dose. A prescription dose of 42.5 Gy in 16 fractions was applied for all planning techniques. Each treatment plan was created to meet the planning goals defined in Table 2.

1) 3DCRT and 3DFIF planning

3DCRT plans involved a pair of tangential fields with parallel opposing posterior fields and the choices of gantry angles for 3DCRT plans were selected to provide best PTV dose coverage while minimizing as much exposure as possible to adjacent OARs. Dynamic wedge angles and weightings used were selected to give the best PTV dose coverage and homogeneity. For all 3DCRT plans, 6-MV beams were used. Corresponding 3DFIF plan was created using the same gantry and collimator angles as 3DCRT plan for each patient CT dataset. One to two subfields were incorporated and shaped using multi-leaf collimators (MLCs) to remove any hot spots. For breast separation >23 cm, 18-MV beams were included as subfield(s) to produce increased PTV dose coverage.

2) Ecomp planning

Ecomp plans were generated with the same tangential fields' arrangement used in both 3DCRT and 3DFIF plans for each patient CT dataset. Addition of fluence was performed by incorporating irregular surface compensator for each tangential field. Selection of tissue penetration depth (TPD) for each irregular surface compensator was dependent on each patient's breast separation. Skin flash was added for both fields to provide additional fluence beyond the skin surface. If required, manual fluence editing was also performed on case by case.

3) Hybrid planning

Hybrid plan consisted of a pair of open tangents supplemented with a pair of IMRT tangents with the same field parameters. Plan was normalized to 100% at reference point and manual fluence editing done as necessary.

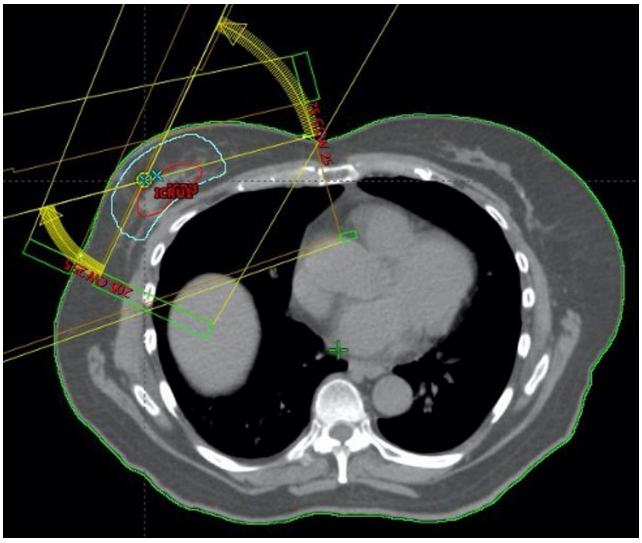


Fig. 1. Tangential 50° arcs in tangential volumetric modulated arc therapy plan. Each arc travels in opposing direction to each other (clockwise and anti-clockwise) to deliver dose to the entire breast volume.

4) tIMRT and IMRT MF5 planning

Gantry angles and field parameters for tIMRT plans were similar to Ecomp and the objective functions were specified accordingly to achieve the planning goals. For IMRT MF5 plans, 3 additional fields were incorporated in addition to the medial and lateral tangential fields, resulting in a total of 5 fields. Gantry angles were individually selected for each patient CT dataset to achieve optimal target coverage and minimize entry and exit dose to ipsilateral lung (IL), contralateral lung (CL), CB, and heart. Similar to tIMRT plan, IMRT MF5 plan was also optimized with objective functions specified to achieve the best attainable plan. Post-optimization improvements such as removal of hot spots, increasing PTV coverage and minimizing OARs dose were performed through manual fluence editing.

5) tVMAT planning

tVMAT plan utilized tangential with 50° dual arcs (Fig. 1). The gantry angles were chosen to achieve optimal PTV coverage and minimum OAR doses. Objective functions were specified accordingly to achieve plan objectives and dose constraints as illustrated in Table 2.

3. Plan comparison and statistical analysis

The parameters used for comparison of all plans were as shown in Table 3. Conformity Index (CI) and Homogeneity Index (HI) were

https://doi.org/10.3857/roj.2020.00619

Table 3. Plan evaluation parameters for PTV, IL, CL, CB, heart, liver, MUs and the body

	Plan evaluation parameters
PTV	Conformity Index (CI)
	Homogeneity Index (HI)
	Maximum PTV dose (PTV_{Dmax})
	Percentage volume of PTV receiving 95% dose ($PTV_{V95\%}$)
IL	Mean IL dose (IL_{Dmean})
	Percentage volume of IL receiving 5 Gy (IL_{V5Gy})
	Percentage volume of IL receiving 20 Gy (IL_{V20Gy})
	Percentage volume of IL receiving 30 Gy (IL_{V30Gy})
CL	Mean CL dose (CL_{Dmean})
	Percentage volume of CL receiving 10 Gy (CL_{V10Gy})
CB	Maximum CB dose (CB_{Dmax})
	Mean CB dose (CB_{Dmean})
	Percentage volume of CB receiving 5 Gy (CB_{V5Gy})
Heart	Mean heart dose ($Heart_{Dmean}$)
	Percentage volume of heart receiving 5 Gy ($Heart_{V5Gy}$)
	Percentage volume of heart receiving 20 Gy ($Heart_{V20Gy}$)
Liver	Mean liver dose ($Liver_{Dmean}$)
	Percentage volume of liver receiving 10 Gy ($Liver_{V10Gy}$)
MUs	Total MUs
Body	Percentage volume of body receiving 10 Gy ($Body_{V10Gy}$)

PTV, planning target volume; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast; MUs, monitor units.

calculated using the following formulas:

$$CI = \frac{V_{RI}}{TV},$$

$$HI = \frac{D_5}{D_{95}}$$

V_{RI} represents PTV volume in cm^3 receiving 41.38 Gy or 95% of prescribed dose and TV represents PTV volume in cm^3. D_5 is minimum dose delivered to 5% of PTV and D_{95} is the minimum dose of 95% of PTV.

IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis to compare dosimetric parameters. One-way analysis of variance (ANOVA) tests were done to evaluate the dosimetric differences between all 7 techniques and post-hoc analysis was performed using Tukey's honestly significant difference (HSD) test. Interactions between the planning techniques and breast volumes ($<1,000$ cm^3 and $>1,000$ cm^3) were also evaluated using two-way ANOVA and Tukey's HSD test for post-hoc analysis. Differences were considered as statistically significant when p-value is <0.05.

Results

A total of 30 patients were included in this study, all diagnosed with early-stage malignant neoplasm of the breast prior to treatment. Age range of patients was between 34 and 78 years old. Outcomes for the PTV and OARs dosimetric parameters are shown in Table 4.

1. PTV dosimetry

There was a significant difference ($p < 0.001$) in PTV_{Dmax} amongst all techniques. PTV_{Dmax} was significantly higher in 3DCRT, IMRT MF5, and tVMAT ($p < 0.001$), and above the limit of 107%. The difference among all 7 techniques in terms of $PTV_{V95\%}$ was statistically significant ($p < 0.05$). Significantly lower $PTV_{V95\%}$ was observed in tVMAT ($p < 0.05$) compared to other 6 techniques. CI was found to be significantly different ($p < 0.05$) among all techniques. tVMAT resulted in the significantly lower CI ($p < 0.05$) compared to all other techniques.

A significant difference ($p < 0.001$) was observed in terms of HI amongst all 7 techniques. Statistically significantly higher HI, hence poorer PTV dose homogeneity in 3DCRT, IMRT MF5, and tVMAT ($p < 0.001$) were observed when compared to the other techniques. Ecomp was also found to have the best PTV dose homogeneity as demonstrated by the HI value being closest to 1.0.

Breast volumes of each patient CT dataset was categorised into two groups: $<1,000$ cm^3 and $>1,000$ cm^3 to identify dosimetric differences on PTV dose conformity based on CI and dose homogeneity based on HI, as a result of interactions between the various techniques and breast volumes. It was shown that there was no statistically significant interaction between the effects of techniques and breast volumes on PTV dose conformity ($p = 0.859$) (Table 5, Fig. 2). Like PTV dose conformity, no significant interaction between the effects of techniques and breast volumes was identified on PTV dose homogeneity ($p = 0.550$) (Table 5, Fig. 3).

2. Ipsilateral lung dosimetry

Difference in IL_{Dmean} between the 7 techniques was found to be significant ($p < 0.001$). tVMAT had significantly highest IL_{Dmean}, followed by IMRT MF5 ($p < 0.001$ for both) compared to other techniques. No significant difference was observed among techniques with tangential beams.

For IL_{V5Gy}, it was also found to have significant difference among all techniques ($p < 0.001$). IL_{V5Gy} showed significantly highest for IMRT MF5 followed by tVMAT ($p < 0.001$ for both). Between IMRT MF5 and tVMAT, IMRT MF5 resulted in significantly higher IL_{V5Gy} ($p < 0.001$).

Difference in IL_{V20Gy} among all techniques was statistically signif-

Table 4. Dosimetric parameter outcomes for PTV and OARs, along with required planning times required between the various techniques

Parameter	3DCRT	3DFIF	IMRT MF5	tIMRT	tVMAT	Ecomp	Hybrid
PTV_{Dmax} (Gy)	46.01 ± 1.52	45.07 ± 0.36	46.38 ± 0.53	45.03 ± 0.69	46.35 ± 0.70	44.61 ± 0.71	44.87 ± 0.59
$PTV_{V95\%}$ (%)	98.19 ± 2.80	97.97 ± 3.02	99.05 ± 1.32	98.79 ± 2.01	95.73 ± 4.24	98.24 ± 2.69	98.59 ± 2.38
Conformity Index	0.98 ± 0.03	0.98 ± 0.03	0.99 ± 0.01	0.99 ± 0.02	0.96 ± 0.04	0.98 ± 0.03	0.98 ± 0.03
Homogeneity Index	1.09 ± 0.03	1.08 ± 0.03	1.10 ± 0.01	1.06 ± 0.03	1.11 ± 0.03	1.06 ± 0.03	1.07 ± 0.03
IL_{Dmean} (Gy)	4.81 ± 2.48	4.70 ± 2.37	8.21 ± 1.01	4.86 ± 1.96	8.97 ± 2.24	5.18 ± 2.56	5.36 ± 2.38
IL_{V5Gy} (%)	15.44 ± 7.84	15.61 ± 7.88	57.62 ± 9.20	16.84 ± 7.34	43.51 ± 9.87	17.50 ± 8.74	18.07 ± 8.35
IL_{V20Gy} (%)	8.61 ± 5.69	8.58 ± 5.64	9.13 ± 3.79	9.23 ± 5.24	16.68 ± 5.64	9.94 ± 6.57	10.44 ± 6.51
IL_{V30Gy} (%)	7.18 ± 5.24	7.06 ± 5.13	2.77 ± 2.09	6.44 ± 3.88	9.65 ± 4.50	7.37 ± 5.83	7.92 ± 5.05
CL_{Dmean} (Gy)	0.04 ± 0.03	0.04 ± 0.03	4.00 ± 1.56	0.04 ± 0.03	0.47 ± 0.32	0.05 ± 0.03	0.06 ± 0.03
CL_{V10Gy} (%)	0 ± 0	0 ± 0	10.38 ± 6.84	0 ± 0	0.23 ± 0.55	0 ± 0	0 ± 0
CB_{Dmax} (Gy)	8.02 ± 12.74	7.87 ± 12.03	22.00 ± 11.46	7.25 ± 11.47	27.61 ± 7.39	8.20 ± 12.64	9.29 ± 13.34
CB_{Dmean} (Gy)	0.16 ± 0.12	0.17 ± 0.12	2.49 ± 1.83	0.14 ± 0.13	2.30 ± 2.08	0.18 ± 0.15	0.30 ± 0.53
CB_{V5Gy} (%)	0.12 ± 0.39	0.16 ± 0.53	14.52 ± 17.11	0.13 ± 0.43	14.86 ± 15.68	0.17 ± 0.50	0.18 ± 0.51
$Heart_{Dmean}$ (Gy)	1.52 ± 1.14	1.51 ± 1.11	4.20 ± 0.66	1.80 ± 0.74	4.98 ± 1.63	1.91 ± 0.96	2.15 ± 1.03
$Heart_{V5Gy}$ (%)	2.97 ± 3.48	2.79 ± 3.11	23.90 ± 6.62	4.28 ± 3.03	25.28 ± 8.24	4.63 ± 3.76	5.00 ± 3.96
$Heart_{V20Gy}$ (%)	1.45 ± 2.26	1.45 ± 2.26	1.12 ± 2.07	1.99 ± 1.95	6.80 ± 4.19	2.58 ± 2.52	2.89 ± 2.77
$Liver_{Dmean}$ (Gy)	1.22 ± 1.78	1.20 ± 1.72	6.56 ± 4.02	1.48 ± 1.30	4.23 ± 3.05	1.69 ± 1.61	1.82 ± 1.48
$Liver_{V10Gy}$ (%)	1.73 ± 4.19	1.76 ± 4.21	27.00 ± 20.02	3.00 ± 3.54	12.89 ± 10.27	3.27 ± 3.91	3.55 ± 3.94
$Body_{V10Gy}$ (%)	8.07 ± 2.08	8.12 ± 2.10	16.71 ± 3.65	8.84 ± 1.82	13.40 ± 2.71	9.13 ± 1.97	9.29 ± 1.97
Total MUs	311 ± 21	303 ± 15	142 ± 19	500 ± 78	364 ± 49	520 ± 42	465 ± 53
Planning time (min)	14 ± 2	16 ± 3	80 ± 14	16 ± 2	39 ± 2	15 ± 3	18 ± 2

Values are presented as mean ± standard deviation.
PTV, planning target volume; OAR, organs-at-risk; 3DCRT, three-dimensional conformal radiation therapy; 3DFIF, three-dimensional field-in-field; IMRT MF5, 5-field intensity-modulated radiotherapy; tIMRT, tangential IMRT; tVMAT, tangential volumetric modulated arc therapy; Ecomp, electronic tissue compensation; IL, ipsilateral lung; CL, contralateral lung; CB, contralateral breast; MUs, monitor units.

Table 5. Comparison of PTV Conformity Index (CI) and Homogeneity Index (HI)

Technique	CI (p = 0.859)		HI (p = 0.550)	
	Breast volume < 1,000 cm^3	Breast volume > 1,000 cm^3	Breast volume < 1,000 cm^3	Breast volume > 1,000 cm^3
3DCRT	0.97 ± 0.04	0.99 ± 0.02	1.09 ± 0.03	1.09 ± 0.04
3DFIF	0.98 ± 0.03	0.98 ± 0.03	1.07 ± 0.02	1.08 ± 0.04
IMRT MF5	0.99 ± 0.01	0.99 ± 0.01	1.10 ± 0.01	1.09 ± 0.01
tIMRT	0.99 ± 0.02	0.99 ± 0.02	1.06 ± 0.03	1.07 ± 0.03
tVMAT	0.95 ± 0.04	0.96 ± 0.05	1.12 ± 0.03	1.11 ± 0.03
Ecomp	0.98 ± 0.03	0.99 ± 0.03	1.06 ± 0.03	1.06 ± 0.03
Hybrid	0.98 ± 0.02	0.099 ± 0.03	1.07 ± 0.03	1.08 ± 0.03

Values are presented as mean ± standard deviation.
PTV, planning target volume; 3DCRT, three-dimensional conformal radiation therapy; 3DFIF, three-dimensional field-in-field; IMRT MF5, 5-field intensity-modulated radiotherapy; tIMRT, tangential IMRT; tVMAT, tangential volumetric modulated arc therapy; Ecomp, electronic tissue compensation.

icant ($p < 0.001$). Statistically significantly higher IL_{V20Gy} was found in tVMAT ($p < 0.001$) in comparison to other techniques. The difference among all techniques was statistically significant for IL_{V30Gy} ($p < 0.001$). IMRT MF5 showed significantly reduced IL_{V30Gy} ($p < 0.05$) in comparison to other techniques.

3. Contralateral lung dosimetry

The difference among all techniques in terms of CL_{Dmean} was statistically significant ($p < 0.001$). IMRT MF5 was found to result in statistically significantly higher CL_{Dmean} ($p < 0.001$) compared to other techniques, close to 100 times higher than techniques with tangential fields arrangement. tVMAT followed as the second highest in terms of CL_{Dmean} and was approximately 10 times higher than 3DCRT, 3DFIF, tIMRT, Ecomp, and Hybrid. Among techniques using tangential fields arrangement, no significant difference was observed.

https://doi.org/10.3857/roj.2020.00619

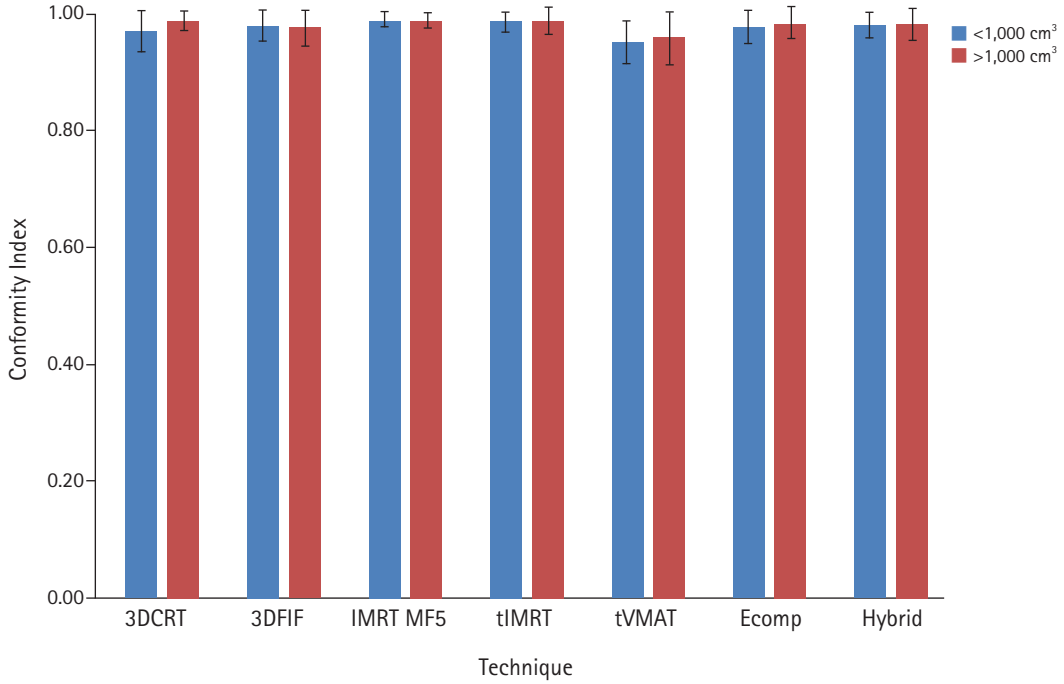


Fig. 2. Mean Conformity Index (CI) of all 7 techniques according to breast volumes. Error bars represent ±1 standard deviation. Black line over bars represents CI of 1.0 that represents ideal dose conformity to planning target volume. 3DCRT, three-dimensional conformal radiation therapy; 3DFIF, three-dimensional field-in-field; IMRT MF5, 5-field intensity-modulated radiotherapy; tIMRT, tangential IMRT; tVMAT, tangential volumetric modulated arc therapy; Ecomp, electronic tissue compensation.

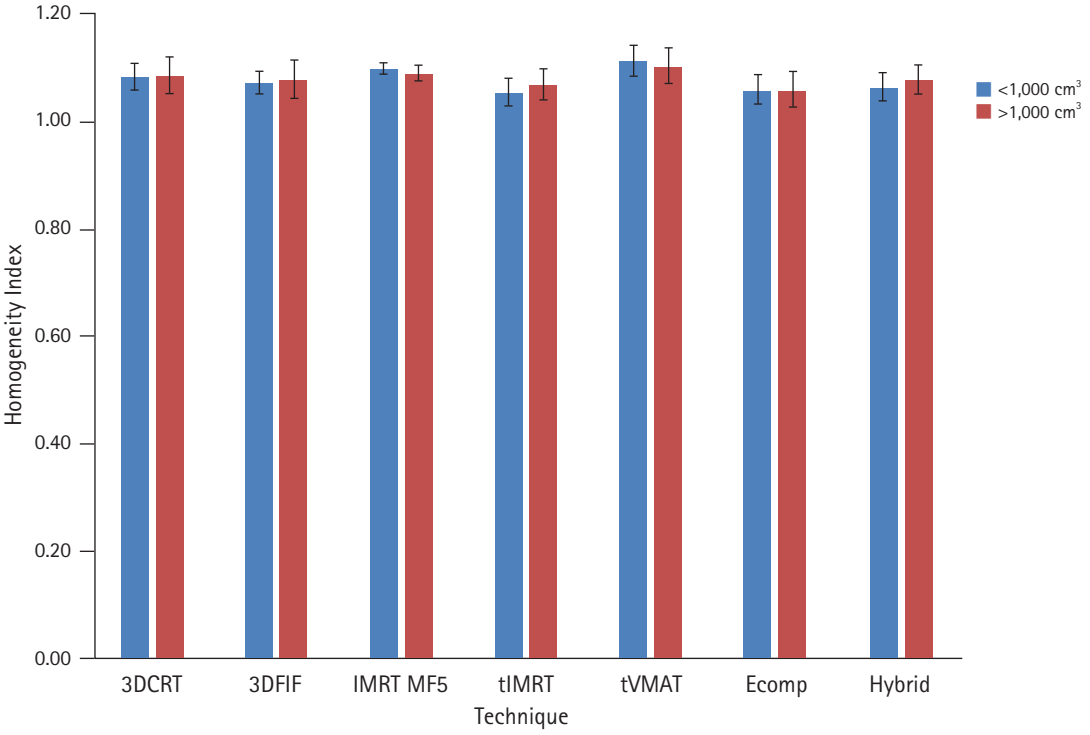


Fig. 3. Mean Homogeneity Index (HI) of all 7 techniques according to breast volumes. Error bars represent ±1 standard deviation. Black line over bars represents HI of 1.0 that represents ideal dose homogeneity in planning target volume. 3DCRT, three-dimensional conformal radiation therapy; 3DFIF, three-dimensional field-in-field; IMRT MF5, 5-field intensity-modulated radiotherapy; tIMRT, tangential IMRT; tVMAT, tangential volumetric modulated arc therapy; Ecomp, electronic tissue compensation.

Similar to CL_{Dmean}, difference in CL_{V10Gy} was also statistically significant among all techniques ($p < 0.001$). IMRT MF5 produced significantly increased CL_{V10Gy} ($p < 0.001$) compared to others.

4. Contralateral breast dosimetry

Difference among the 7 techniques was statistically significant ($p < 0.001$) for CB_{Dmax}. Both tVMAT and IMRT MF5 ($p < 0.001$ for both) resulted in statistically significantly increased CB_{Dmax}. However, both were not significantly different to each other. There was also no statistically significant difference in CB_{Dmax} demonstrated between the techniques with tangential beams.

CB_{Dmean} of all techniques were significantly different ($p < 0.001$). CB_{Dmean} was significantly higher in IMRT MF5 and tVMAT ($p < 0.001$ for both) compared to other techniques, however both were not different from each other.

CB_{V5Gy} of all techniques were also shown to be statistically significantly different ($p < 0.001$). tVMAT and IMRT MF5 ($p < 0.001$ for both) resulted in almost 100 times significantly higher CB_{V5Gy} compared to other 5 techniques with tangential beams, however, were not significantly different from each other.

5. Heart dosimetry

The difference in $Heart_{Dmean}$ among all 7 techniques was statistically significant ($p < 0.001$). Statistically significantly increased $Heart_{Dmean}$ was observed in tVMAT and IMRT MF5 ($p < 0.001$ for both) and were beyond the dose tolerance goal limit of 4 Gy. However, no significant difference was observed between both techniques. Between techniques with tangential fields arrangement, no statistically significant difference was found.

In terms of $Heart_{V5Gy}$, the difference between all techniques was also significant ($p < 0.001$). Significantly higher $Heart_{V5Gy}$ in tVMAT and IMRT MF5 ($p < 0.001$ for both) were observed, approximately 5 to 10 times greater than other 5 techniques.

For $Heart_{V20Gy}$, the difference among all techniques was significant ($p < 0.001$). tVMAT demonstrated significantly highest $Heart_{V20Gy}$ compared to other techniques ($p < 0.001$).

6. Liver dosimetry

IMRT MF5 resulted in significantly higher $Liver_{Dmean}$ ($p < 0.001$) compared to 3DCRT, 3DFIF, tIMRT, Ecomp, and Hybrid. tVMAT ($p < 0.05$) also had significantly higher $Liver_{Dmean}$ compared to 3DCRT and 3DFIF, however was not significantly different from tIMRT, Ecomp, Hybrid, and IMRT MF5. The remaining 5 techniques adopting the tangential fields configuration showed similar $Liver_{Dmean}$ and were not significantly different from each other.

$Liver_{V10Gy}$ was also significantly different between the various techniques ($p < 0.001$). IMRT MF5 demonstrated statistically significantly highest $Liver_{V10Gy}$ among all techniques ($p < 0.05$). tVMAT ($p < 0.05$) also had significantly higher $Liver_{V10Gy}$ compared to 3DCRT and 3DFIF, however was not statistically significantly different from other intensity-modulated techniques—tIMRT, Ecomp, and Hybrid. Reduced $Liver_{V10Gy}$ was observed among techniques with tangential beams, however no significant difference was observed among them.

7. Total monitor units, body low dose and planning time comparisons

Difference in total monitor units (MUs) produced by all 7 techniques was statistically significant ($p < 0.001$). Statistically significantly highest total MUs was observed in IMRT MF5 ($p < 0.001$). 3DCRT, 3DFIF, and tVMAT were shown to produce significantly lower total MUs ($p < 0.001$ for all three) but were not significantly different from each other. Those utilizing intensity-modulated beams (tIMRT, Ecomp and Hybrid), resulted in significantly higher total MUs ($p < 0.001$ for all three). However, they were also not significantly different from each other.

Statistically significant increase in $Body_{V10Gy}$ of approximately twice the amount was observed in IMRT MF5 and tVMAT ($p < 0.001$ for both) among all techniques.

To evaluate the efficiency of each technique, planning times for the various techniques were also recorded and compared (Table 4). Planning times for all studied techniques were significantly different ($p < 0.001$). Among all techniques, IMRT MF5 required the longest planning time followed by tVMAT ($p < 0.001$ for both). IMRT MF5 was significantly longer ($p < 0.001$) to plan than tVMAT. 3DCRT and Ecomp were techniques with shortest planning times.

Discussion and Conclusion

To date, no study had been carried out that performed a direct comparison of conventional 3DCRT and 3DFIF with more advanced techniques: Ecomp, Hybrid technique, various numbers of IMRT beams and use of tangential arc arrangements in VMAT, as part of an entire study of radiation therapy to both left and right early-stage breast cancer cases. In this study, PTV and OARs dosimetries were used as parameters for direct comparison between 3DCRT, 3DFIF, IMRT MF5, tIMRT, tVMAT, Ecomp, and Hybrid techniques.

It is essential that PTV_{Dmax} is kept to <107% (45.48 Gy) to achieve the desired dose uniformity eventually to reduce risk of skin reactions. Results obtained in this study demonstrated that only 3DFIF, tIMRT, Ecomp, and Hybrid were able to meet the constraint of PTV_{Dmax} <107%, with Ecomp having the lowest PTV_{Dmax}.

IMRT MF5 produced highest $PTV_{V95\%}$ compared to other tech-

https://doi.org/10.3857/roj.2020.00619

niques, indicating improved dose coverage. This was consistent with the findings in some studies that increasing number of IMRT beams would increase PTV dose coverage [13-15]. As PTV CI is directly correlated to $PTV_{V95\%}$, it was hence not surprising that IMRT MF5 also similarly showed highest CI among all techniques. Despite having the highest $PTV_{V95\%}$ and CI value closest to the ideal value of 1.0, IMRT MF5 did not show any significant difference in comparison with techniques using tangential beams. This indicates that although increasing number of beams as seen in IMRT MF5 showed increased $PTV_{V95\%}$ and CI, it is however comparable to techniques using only tangential beams.

tVMAT showed the statistically significantly worst performance for $PTV_{V95\%}$ and CI. This was in contrary to the findings reported by Zhao et al. [16], Lin et al. [17], and Qiu et al. [18] that VMAT resulted in improved CI than IMRT and 3DCRT plans. This discrepancy can be attributed to the varied arc arrangement used in this study compared to those used by the above-mentioned studies. As a matter of fact, Viren et al. [19] found that use of a pair of 50° dual arcs, similar to that used in this study, resulted in lower target dose coverage and conformity compared to the use of continuous arc arrangement employed by most studies.

Previous reports stated Ecomp as providing improved target dose homogeneity, especially over the conventional 3DCRT [20-22]. This was observed as true in this study, with Ecomp producing the best HI among all techniques, having the value closest to the ideal value of 1.0. Zaghloul et al. [23] reported a correlation between improved PTV HI and significant reduction of acute skin reaction incidence. This correlation between the clinical outcome and PTV HI can be applicable to the findings in this study that indicates Ecomp as having the potential of reducing risk of acute skin toxicities compared to the other techniques. In contrast, tVMAT and IMRT MF5 were observed to give statistically significantly poorest PTV HI. Poorer PTV dose homogeneity observed in both tVMAT and IMRT MF5 could be due to number of beams and the configurations of arcs and beams used. The use of optimizer and OARs constraint-based process involved, could have also further contributed to the overall poorer PTV dose homogeneity. In the attempt of meeting the OARs dose constraint, optimization-convergence errors were likely to have occurred [24], especially due to the major tissue density difference present between the breast tissue and air in the lungs. Thus, in the optimizer's attempt of achieving various constraints of OARs that also included the low-density lungs, heterogenous regions of high and low doses (hot and cold spots) were formed within the PTV.

Previous studies also reported a correlation in breast volume and dose homogeneity [25-27]. Large breast volumes tend to involve reduced dose homogeneity and increased high dose regions within the PTV that result in acute skin toxicity [15,26]. In this study, it was found that there was no statistically significant interaction between the effects of variations in breast volumes and techniques on both CI and HI. However, there were significant differences on PTV CI and HI between various techniques. This indicates that only variations in techniques affect CI and HI, and that they do not vary according to breast volumes.

In this study, IMRT MF5 had the highest IL_{V5Gy} and lowest IL_{V30Gy} among all techniques. These findings corroborate with the data reported by Liu et al. [28] that showed 5-field IMRT was able to reduce the IL_{V20Gy} and IL_{V30Gy} in comparison to 3DCRT with tangential beams. In terms of CL exposure, IMRT MF5 also showed significantly highest CL_{Dmean} and CL_{V10Gy}. Such findings are similar to that presented by Rongsriyam et al. [29] in which CL_{Dmean} was also found to be much higher in IMRT than in 3DCRT. These results were expected due to greater number of beams involved that resulted in increased beam entry and exit through CL, hence the dose contribution. This implies that success of IMRT MF5 in reducing the volumes of lungs receiving high doses comes at the expense of overall higher mean dose and greater volumes receiving the low dose.

Use of arcs in VMAT in previous studies [14,30] was similarly found to result in significantly higher low-dose volume, especially to IL, which is also observed in this present study. In general, this highlights that non-tangential beams techniques result in increased lungs exposure, thus greater implication in future development of pulmonary complications. Techniques with tangential beams are in contrast, comparably similar to each other in improving lung sparing, hence reducing the likelihood of radiation pneumonitis and secondary lung cancer post-radiotherapy.

Some studies have reported that IMRT reduced the CB dose compared to conventional 3DCRT [31,32]. This was found to be true in this study, with tIMRT showing lower CB doses than 3DCRT. However, it is not the case for IMRT MF5 due to greater number of fields used that resulted in low dose spill to greater CB volume. This can be of high importance, especially to patients <40 years old who are at greater risk of secondary CB cancer [33]. Similar to the results in this study, other papers have also reported that use of VMAT resulted in high low-dose volume to CB [14,34], hence also posing the issue of greater risk of inducing secondary CB cancers especially to younger patients. The application of techniques with tangential beams in contrast, introduces a greater advantage of improved CB dosimetry, thus reduced risk of inducing secondary CB cancers.

In this study, all studied techniques were able to meet the constraint of $Heart_{Dmean}$ of <4 Gy, except for IMRT MF5 and tVMAT. Both the above techniques were also found to result in higher $Heart_{V5Gy}$ compared to the rest. These findings are similar to those

by Liu et al. [28] who found that 5-field IMRT and double-arcs VMAT both had higher heart doses compared to 3DCRT. This present study showed reduced heart doses with in techniques utilizing tangential beams, hence once again highlighting the advantage of improved organ sparing compared to the use of multi-fields or arcs utilizing techniques.

Radiation-induced liver disease (RILD) is often described as a significant complication and major limitation of liver cancer radiation treatment [35]. Although the whole liver is not directly irradiated in breast radiation therapy, liver toxicity is a factor that must still be taken into consideration in right-sided breast radiation therapy due to its close proximity to PTV. In this study, the number of right-sided patient cases is less than left-sided cases, however the results positively showed a significant reduction of liver doses in 3DCRT, 3DFIF, tIMRT, Ecomp, and Hybrid compared to IMRT MF5 and tVMAT. Higher liver doses observed in IMRT MF5 and tVMAT can be attributed to greater low dose volume caused by increased number of intensity-modulated fields, greater field scattering and dose leakage between the MLC leaves [28]. Techniques utilizing tangential beams are in contrast better for liver sparing and thus able to reduce the risk of RILD.

IMRT MF5 showed significantly highest total MUs, almost 5 times of the conventional 3DCRT and 3DFIF. Other techniques similarly using intensity-modulated fields (tIMRT, tVMAT, Ecomp, and Hybrid) also showed higher MUs than 3DCRT and 3DFIF. This was expected because intensity-modulated techniques involve large numbers of small subfields to achieve optimum intensity distributions of each treatment field [36], thus resulting in higher MUs compared to non-intensity modulated 3DCRT and 3DFIF. With increase in the number of intensity-modulated beams, it was not surprising that IMRT MF5 resulted in highest total MUs.

In this study, IMRT MF5 had the highest $Body_{V10Gy}$ followed by tVMAT. Involvement of more beams and therefore larger volume of normal tissues exposed to the low dose as demonstrated with higher $Body_{V10Gy}$ was thus expected of IMRT MF5. Although tIMRT, Ecomp, and Hybrid are also intensity-modulated techniques, the lower MUs involved provided the advantage of lower $Body_{V10Gy}$ that are comparable to conventional 3DCRT, hence pose no increased risk of inducing secondary cancers compared to conventional 3DCRT and 3DFIF.

tVMAT has lower MUs than all other intensity-modulated techniques and is similar to that of 3DCRT and 3DFIF. However, it still resulted in second highest $Body_{V10Gy}$. This finding is attributed to the arc motion that produces dose fall-off occurring in every direction, therefore distributing low doses to bigger volumes of normal tissues, resulting in subsequent increased risk of secondary cancer induction. This observation is similar to a study conducted by Abo-Madyan et al. [37] who found that in comparison with 3DCRT, VMAT resulted in higher cumulated excess absolute risk of developing secondary malignancies after exposure to low doses. Based on the analysis, use of tIMRT, Ecomp, and Hybrid as alternatives to 3DCRT and 3DFIF pose no increased risk of inducing secondary malignancies due to comparable smaller body volumes receiving low doses. IMRT MF5 and tVMAT however, can potentially increase the risk due to greater body volume exposed to low doses.

A large number of early-stage breast cancer patients is often observed in a typical radiation therapy department. This implies that techniques with increasing complexity will affect the department's resource allocation. To determine the department's resource efficiency, parameters such as treatment and planning times were often used [38]. Under clinical setting, total MUs are associated with treatment time. Though this study is a planning study that does not constitute treatment delivery, the results suggest that IMRT MF5 is the technique that would require longest treatment time while techniques with lowest MUs (3DCRT, 3DFIF and tVMAT) would result in shortest treatment time.

In terms of planning time, this study similarly revealed that IMRT MF5 requires the longest time followed by tVMAT. This was due to the process of adjusting the field and arc arrangements, along with iterative optimization processes to achieve the best plans. Planning times for tIMRT and Ecomp are in contrast, comparable to conventional 3DCRT and 3DFIF. However, as tIMRT requires inverse-planning, similar to IMRT MF5, tVMAT and Hybrid, additional steps of contouring of the IMRT structures are required for the optimization process. The planning times recorded for these inverse-planned techniques in this study do not include the duration required to contour those IMRT structures. Since Ecomp is a forward-planned technique, that additional time of contouring the IMRT structures is not required, hence is more superior than the other advanced techniques in terms of time-efficiency. When looking at studies published on Ecomp, it was also suggested that electronic compensation algorithm used for Ecomp is a feature found only in Eclipse TPS. Hence, institutions using other TPS might not be able to implement the use of Ecomp as an alternative WBRT technique.

Based on the analyses, techniques with tangential beams result in significant reduction of OARs doses compared to those using multiple beams and arcs as demonstrated in IMRT MF5 and tVMAT. In terms of PTV dose coverage, conformity and homogeneity, tIMRT, Ecomp, and Hybrid are more superior than 3DCRT and 3DFIF and are also comparable to conventional 3DCRT and 3DFIF in the OARs doses. However, it is noted that Hybrid led to higher contribution of low-doses to IL, CL, CB, heart, and liver compared to tIMRT and Ecomp, indicating a possible clinical significance of increased risk of long-term complications and secondary cancer induction. This

 https://doi.org/10.3857/roj.2020.00619

was similarly observed in the studies conducted by Mayo et al. [39] and Xie et al. [40] who found that improvements of PTV dosimetry in Hybrid were achieved at the expense of increased low-dose volume to the CB, lungs and heart compared to tangential IMRT-only technique.

Out of the three, Ecomp required comparably shorter planning time. Use of skin flash tool incorporated in Ecomp also further helps to account for patient's breathing motion, increasing the accuracy of dose delivery. Overall, this highlights the potentially better patient outcome and subsequently improved patient's QOL. Therefore, Ecomp shows promising use in terms of efficiency and effectiveness and may be favoured as an optimal technique for WBRT in departments where Eclipse planning system is available.

This study focusses exclusively on early-stage breast cancer patients treated with WBRT without any regional lymph nodes involvement. Hence, the current results might not be applicable for patients requiring treatments to both breast and the regional nodes. A greater number of patient cases and inclusion of patient groups requiring breast and nodal radiation therapy should therefore be done in future studies to better evaluate the results and draw more definitive conclusions.

In conclusion, techniques with tangential fields arrangement resulted in overall better OARs dosimetry compared to those with multi-fields and arcs arrangements. Of all the techniques used in this study, Ecomp emerged as a better treatment technique for WBRT in terms of both effectiveness and efficiency. However, this study is a retrospective planning study and therefore the planning dosimetric data obtained might be different from actual delivered doses to patients in real-life clinical situations. Further studies involving water phantom simulation and/or clinical applications on patients are hence required to better compare and verify the dosimetric results obtained in this study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

The authors acknowledge the support given by the Medical Radiations Discipline in the School of Health and Biomedical Sciences at RMIT University, Australia.

References

1. Cancer Australia. What is breast cancer? [Internet]. Strawberry Hills, Australia: Cancer Australia; c2020 [cited 2020 Nov 15]. Available from: https://breast-cancer.canceraustralia.gov.au.
2. International Agency for Research on Cancer. Breast cancer [Internet]. Lyon, France: International Agency for Research on Cancer; c2020 [cited 2020 Nov 15]. Available from: https://gco.iarc.fr/today/fact-sheets-cancers.
3. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer 2013;108:2205-40.
4. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013;24:2206-23.
5. Zurrida S, Veronesi U. Milestones in breast cancer treatment. Breast J 2015;21:3-12.
6. Nantavithya C, Saksornchai K, Oonsiri P, Shotelersuk K. Dosimetric study of three-dimensional conformal radiotherapy, electronic compensator technique, intensity-modulated radiation therapy and volumetric-modulated arc therapy in whole breast irradiation. J Radiother Pract 2017;16:431-43.
7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
8. Tenea Cojan TS, Vidrighin CD, Ciobanu M, et al. Breast-conserving surgery in breast cancer. Chirurgia (Bucur) 2012;107:616-25.
9. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Ann Surg Oncol 2014;21:704-16.
10. Zhang Q, Yu XL, Hu WG, et al. Dosimetric comparison for volumetric modulated arc therapy and intensity-modulated radiotherapy on the left-sided chest wall and internal mammary nodes irradiation in treating post-mastectomy breast cancer. Radiol Oncol 2015;49:91-8.
11. Dayes IS, Whelan TJ, Julian JA, et al. Cross-border referral for early breast cancer: an analysis of radiation fractionation patterns. Curr Oncol 2006;13:124-9.
12. Kara FG, Haydaroglu A, Eren H, Kitapcioglu G. Comparison of different techniques in breast cancer radiotherapy planning. J Breast Health 2014;10:83-7.
13. Popescu CC, Olivotto I, Patenaude V, Wai E, Beckham WA. Inverse-planned, dynamic, multi-beam, intensity-modulated radiation therapy (IMRT): a promising technique when target volume is the left breast and internal mammary lymph nodes. Med Do-

sim 2006;31:283-91.
14. Jin GH, Chen LX, Deng XW, Liu XW, Huang Y, Huang XB. A comparative dosimetric study for treating left-sided breast cancer for small breast size using five different radiotherapy techniques: conventional tangential field, filed-in-filed, tangential-IMRT, multi-beam IMRT and VMAT. Radiat Oncol 2013;8:89.
15. Ayata HB, Guden M, Ceylan C, Kucuk N, Engin K. Comparison of dose distributions and organs at risk (OAR) doses in conventional tangential technique (CTT) and IMRT plans with different numbers of beam in left-sided breast cancer. Rep Pract Oncol Radiother 2011;16:95-102.
16. Zhao H, He M, Cheng G, et al. A comparative dosimetric study of left sided breast cancer after breast-conserving surgery treated with VMAT and IMRT. Radiat Oncol 2015;10:231.
17. Lin JF, Yeh DC, Yeh HL, Chang CF, Lin JC. Dosimetric comparison of hybrid volumetric-modulated arc therapy, volumetric-modulated arc therapy, and intensity-modulated radiation therapy for left-sided early breast cancer. Med Dosim 2015;40:262-7.
18. Qiu JJ, Chang Z, Wu QJ, Yoo S, Horton J, Yin FF. Impact of volumetric modulated arc therapy technique on treatment with partial breast irradiation. Int J Radiat Oncol Biol Phys 2010;78:288-96.
19. Viren T, Heikkila J, Myllyoja K, Koskela K, Lahtinen T, Seppala J. Tangential volumetric modulated arc therapy technique for left-sided breast cancer radiotherapy. Radiat Oncol 2015;10:79.
20. Alghufaili AH, Shanmugarajah L, Kumaraswamy LK. Correlating the depth of compensation to the 3-D shape of the breast to achieve homogeneous dose distribution using the electronic tissue compensation treatment technique. Med Dosim 2019;44:30-4.
21. Hideki F, Nao K, Hiroyuki H, Hiroshi K, Haruyuki F. Improvement of dose distribution with irregular surface compensator in whole breast radiotherapy. J Med Phys 2013;38:115-9.
22. Song Y, Zhang M, Gan L, et al. Predictive parameters for selection of electronic tissue compensation radiotherapy in early-stage breast cancer patients after breast-conserving surgery. Oncotarget 2016;7:32835-45.
23. Zaghloul HA, Rashed YA, Shaukat AA, Rostom YA, Badawy SE. Intensity modulated radiotherapy using multiple in fields compared to wedged fields in breast irradiation: clinical impact on early skin reaction and organs at risk doses. J Nucl Med Radiat Ther 2014;5:176.
24. Lu JY, Zhang JY, Li M, et al. A simple optimization approach for improving target dose homogeneity in intensity-modulated radiotherapy for sinonasal cancer. Sci Rep 2015;5:15361.
25. Moody AM, Mayles WP, Bliss JM, et al. The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. Radiother Oncol 1994;33:106-12.
26. De Langhe S, Mulliez T, Veldeman L, et al. Factors modifying the risk for developing acute skin toxicity after whole-breast intensity modulated radiotherapy. BMC Cancer 2014;14:711.
27. Neal AJ, Torr M, Helyer S, Yarnold JR. Correlation of breast dose heterogeneity with breast size using 3D CT planning and dose-volume histograms. Radiother Oncol 1995;34:210-8.
28. Liu H, Chen X, He Z, Li J. Evaluation of 3D-CRT, IMRT and VMAT radiotherapy plans for left breast cancer based on clinical dosimetric study. Comput Med Imaging Graph 2016;54:1-5.
29. Rongsriyam K, Rojpornpradit P, Lertbutsayanukul C, Sanghangthum T, Oonsiri S. Dosimetric study of inverse-planed intensity modulated, forward-planned intensity modulated and conventional tangential techniques in breast conserving radiotherapy. J Med Assoc Thai 2008;91:1571-82.
30. Zheng H, Lai YQ, Zhou Y, et al. A comparative dosimetric study of seven radiation techniques for breast cancer after mastectomy and immediate breast reconstruction. Transl Cancer Res 2017;6:788-97.
31. Burmeister J, Alvarado N, Way S, et al. Assessment and minimization of contralateral breast dose for conventional and intensity modulated breast radiotherapy. Med Dosim 2008;33:6-13.
32. Bhatnagar AK, Brandner E, Sonnik D, et al. Intensity modulated radiation therapy (IMRT) reduces the dose to the contralateral breast when compared to conventional tangential fields for primary breast irradiation. Breast Cancer Res Treat 2006;96:41-6.
33. Stovall M, Smith SA, Langholz BM, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys 2008;72:1021-30.
34. Osman SO, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol 2014;112:17-22.
35. Kim J, Jung Y. Radiation-induced liver disease: current understanding and future perspectives. Exp Mol Med 2017;49:e359.
36. Seppala J, Lahtinen T, Kolmonen P. Major reduction of monitor units with the avoidance of leaf-sequencing step by direct aperture based IMRT optimisation. Acta Oncol 2009;48:426-30.
37. Abo-Madyan Y, Aziz MH, Aly MM, et al. Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. Radiother Oncol 2014;110:471-6.
38. Smith W, Menon G, Wolfe N, Ploquin N, Trotter T, Pudney D. IMRT for the breast: a comparison of tangential planning techniques. Phys Med Biol 2010;55:1231-41.
39. Mayo CS, Urie MM, Fitzgerald TJ. Hybrid IMRT plans: concurrently treating conventional and IMRT beams for improved breast irradiation and reduced planning time. Int J Radiat Oncol Biol Phys

2005;61:922-32.
40. Xie X, Ouyang S, Wang H, et al. Dosimetric comparison of left-sided whole breast irradiation with 3D-CRT, IP-IMRT and hybrid IMRT. Oncol Rep 2014;31:2195-205.

ROJ Radiation Oncology Journal

Case Report

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):282-286
https://doi.org/10.3857/roj.2020.00577

Primary intracranial leiomyosarcoma presenting with frontal bone mass: a case report

Shaghayegh Kamian[1], Abdolali Ebrahimi[2], Kaveh Ebrahim Zadeh[3], Behnaz Behzadi[4]

[1]*Department of Radiotherapy Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[2]*Department of Pathology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[3]*Department of Neurosurgery, Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[4]*Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received: August 11, 2020
Revised: October 24, 2020
Accepted: November 9, 2020

Correspondence:
Behnaz Behzadi
Department of Radiation Oncology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +989122590051
E-mail: behnaz_bzd@yahoo.com
ORCID:
https://orcid.org/0000-0003-4135-7148

Primary intracranial mesenchymal neoplasms are rare tumors. These tumors are usually metastatic disease from other primary sites. We presented a 31-year-old man with a 6-month history of gradually enlarging frontal mass and positional headache. There was no other symptom demonstrating other organs' involvement. The patient underwent an uncomplicated craniotomy with clear surgical margins. The pathology review and the immunohistochemistry staining confirmed leiomyosarcoma grade II. We prescribed radiation therapy with tumor dose of 60 Gy in 30 fractions with conformal treatment planning to the tumor bed. As this disease has a high potency for metastasis, we advised four courses of single agent doxorubicin chemotherapy 75 mg/m^2 every 4 weeks starting one month after the end of radiotherapy. In the last follow-up visit 34 months later, the patient was disease free in physical exam and imaging findings.

Keywords: Brain neoplasms, Intracranial, Leiomyosarcoma

Introduction

Primary intracranial mesenchymal neoplasms are rare tumors. The majority of intracranial leiomyosarcomas are usually metastatic disease from other primary sites. The common sites of origin are gastrointestinal tract or reproductive system especially in women [1].

Leiomyosarcoma (LMS) as a primary intracranial tumor arise from blood vessels or dura matter mesenchymal cells. These tumors can mimic meningioma on imaging. Primary intracranial LMS is much rare tumor and we could find 16 reported cases till 2018 [1] and two cases in 2019 [2,3] and three cases in 2020 [4-6]. It has been reported to be less than 1% of brain biopsy that was about 3 out of 25,000 primary brain tumors [2].

There are some predisposing factors related to this pathology including radiation exposure [7], immunocompromised states [8], and infections with human immunodeficiency virus (HIV) [9] or Epstein–Barr virus (EBV) [10]. Although there are some reports that this tumor has been seen in immunocompromised patients especially in AIDS [11], the incidence in immune-deficient patients is rare, in general [12]. There are some reports that this pathology has been found in cases who had a history of lung or renal transplantation [8,12]. Also, immunosuppression and radiation induced tumorigenesis have been proposed as probable causative factors for the development of primary intracranial LMS [13].

The symptoms are usually headache, gait disturbance, hemiparesis or seizures. Sometimes this tumor presents with sudden intratumoral hemorrhage [1]. Immunohistochemical staining (IHC) is a helpful tool for discriminate this pathology from the metastasis of other organs or meningioma.

The prognosis of this tumor is poor and the survival range from 3

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

weeks [14] to 44 months [15] in the literature. A standard protocol for the treatment of this disease could not be determined due to the limited number of cases. Surgery remains the mainstay of treatment with the attempt to remove total resection. Radiotherapy and chemotherapy have been used in multiple cases. There are some reports about the use of Gamma Knife radiosurgery in combination with partial surgery with a survival of 3 months [13]. There is limited experience with chemotherapy in this disease [16].

We present a very rare case of primary intracranial LMS who had not immunosuppression and has survived 34 months without any recurrence until the report of this paper despite the poor prognosis reported in the literature.

Case Report

Written informed consent was obtained and signed on the admission of the patient and was kept in his medical files. He declared that his medical information can be used for research purposes in the future and also agree with the provided treatment options.

The patient was a 31-year-old male with a gradually enlarging mass in frontal bone and positional headache, since 6 months before admission. He was visited for the first time in November 2017. There was no other symptom demonstrating other organs' involvement. He did not have any positive note in his past medical and habitual history. In the physical examination, there was a palpable fixed and non-tender mass measuring approximately 3 cm × 2 cm over the left frontal region with no ulcer on the skin. Also, he had small multiple firm, non-tender subdermal lesions on the extremities and trunk compatible with lipoma.

We check blood tests which included complete blood counts and biochemistry which were normal. Also, serology tests for HIV, hepatitis-B virus (HBV), hepatitis-C virus (HCV), and EBV were all negative. In the computerized tomography (CT) scan of the brain, there was a destructive enhancing soft tissue mass measuring 35 mm × 22 mm in left frontal bone and enhancement of the adjacent meninges. The brain magnetic resonance imaging (MRI) showed a 34 mm × 28 mm left frontal skull vault tumoral lesion with high signal intensity in T2 which showed avid enhancement of adjacent dura (Fig. 1). The differential diagnosis with these features in pathology were metastasis, solitary plasmacytoma, hemangiopericytoma and angiosarcoma.

An uncomplicated surgery including mass resection through craniotomy and subsequent cranioplasty was performed on November 13, 2017. The histologic examination demonstrated a high-grade spindle cell neoplasm with invasion of bone and fibro adipose tissue. In the pathologic report, dura matter involvement without adhesion to the bony skull was noted. The surgical margins were tumor free. In the second pathology opinion the diagnosis was high grade pleomorphic sarcoma compatible with anaplastic meningioma. The tumor composed of interlacing bundles of spindle to oval cell with moderate pleomorphism and noticeable mitotic figures (Fig. 2).

In IHC, the tumor was desmin, h-caldesmon, and vimentin positive but immunostaining for epithelial membrane antigen (EMA), progesterone receptor (PR), glial fibrillary acidic protein (GFAP), thyroid transcription factor-1 (TTF-1), calcitonin, melan A, human melanoma black 45 (HMB45), smooth muscle actin (SMA), CD34 and S100 were negative (Figs. 3, 4). The last pathology review and the IHC confirmed leiomyosarcoma grade II.

Following surgery, the patient was referred for radiotherapy to our radiation oncology center. The patient underwent staging workup including chest, abdomen and pelvic CT scan and also

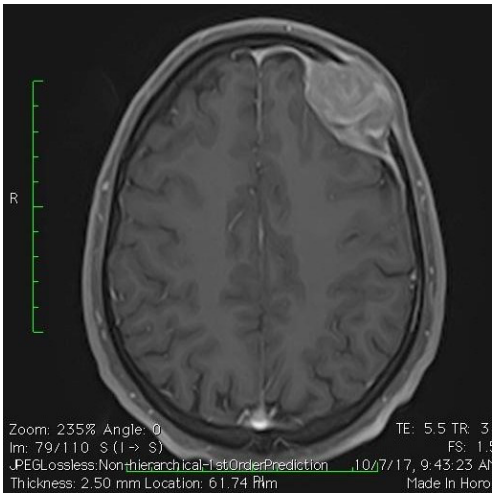


Fig. 1. An axial view of brain magnetic resonance imaging.

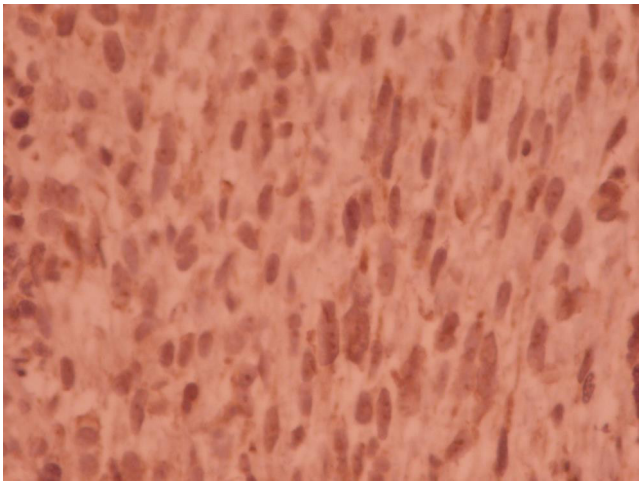


Fig. 2. Immunohistochemistry staining showing h-caldesmon positivity (microscopic image at ×40).

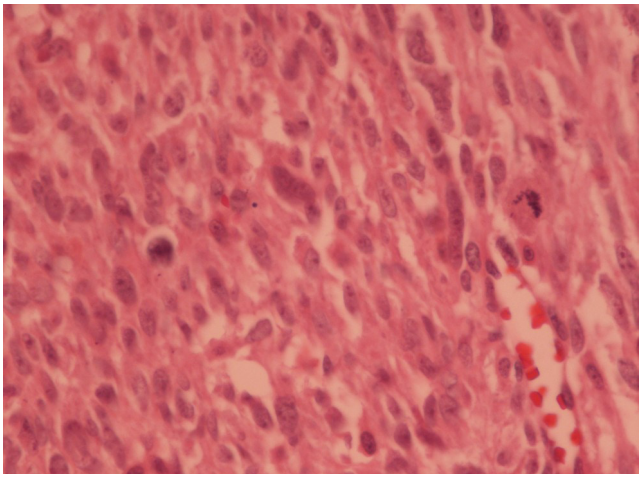


Fig. 3. Interlacing bundles of spindle to oval cells with moderate dysplasia and noticeable mitotic figures (microscopic image at ×40).

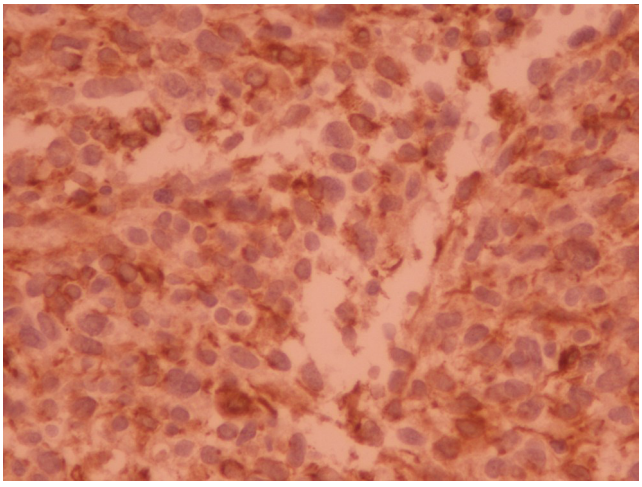


Fig. 4. Immunohistochemistry staining showing vimentin positivity (microscopic image at ×40).

whole-body bone scan. None of the organs outside brain and skull were involved. Also, there was no residue in brain MRI after surgery.

The brain MRI before and after the surgery were fused in the CT simulation and targets were define respect to mass and tumor bed. The isodoses for target volumes are illustrated in Fig. 5. Gross tumor volume (GTV) is in red and planning target volume (PTV) is in blue. We added 1.5-cm margins around the GTV to make clinical target volume (CTV) and 0.5 cm more to define PTV. Treatment planning system was ISOgray edition 4.2.3 (DOSIsoft, Paris, France), and 63 L for conformal treatment planning. Total radiation dose was 60 Gy in 30 fractions.

As this disease has a high potency for metastasis, we advised four cycles of single agent doxorubicin chemotherapy 75 mg/m^2 every 4 weeks starting one month after the end of radiotherapy.

The patient was followed as a common brain tumor with brain MRI every 3 months. But chest, abdomen and pelvic CT scan were also requested every 6 months. In the last visit in August 2020, the patient did not have symptom and sign of disease in the physical examination and also, there was no evidence of disease local recurrence or metastasis in imaging.

Discussion

The prevalence of bone and soft tissue sarcomas is four in 100,000 people per year [17]. LMS is found more frequent in uterus, stomach, intestines or walls of blood vessels. Leiomyosarcomas represent 1%–4% of soft tissue sarcomas of the head and neck [5]. Involvement of central nervous system (CNS) is very infrequent and most of the cases diagnosed as intracranial LMS correspond to

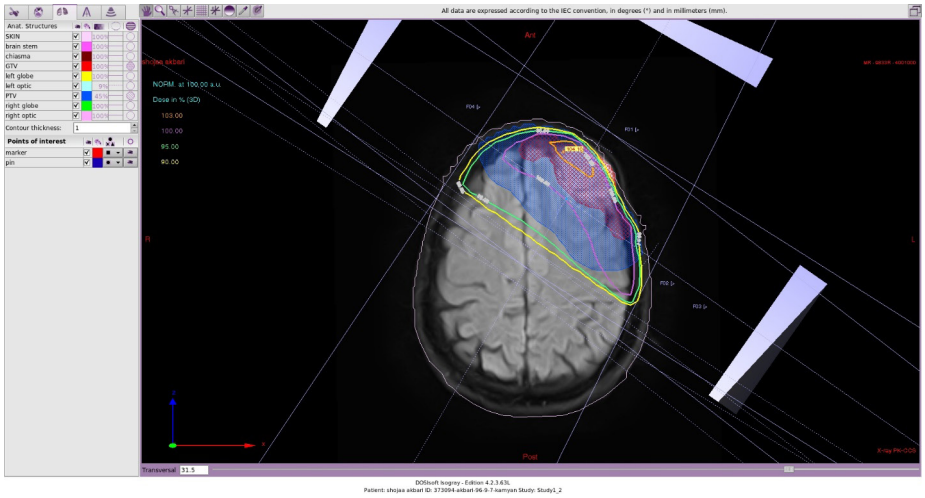


Fig. 5. Target volumes (GTV in red and PTV in blue) and isodoses around target volume (isodose 95% in green and 90% in yellow with maximum hot dose of 105% in the GTV). GTV, gross tumor volume; PTV, planning target volume.

https://doi.org/10.3857/roj.2020.00577

metastatic disease of other primary sites such as the gastrointestinal tract or uterus [5,18,19].

Primary LMS of CNS is extremely rare with reported approximately 21 cases in the world till mid-2020. These tumors can originate from mesenchymal cells in dura matter or blood vessels of brain [16]. There has been an increase in its incidence and reports in recent years, probably associated with HIV infection and better pathological diagnosis of the cases [5]. Sarcoma develops in some patients with brain tumor after radiotherapy or chemotherapy [19]. Previous studies have also reported that LMS is associated with immunodeficiency states caused by EBV or HIV infections [18,20]. The case we reported had no sign or symptom of immunosuppression and the laboratory findings were also all negative for EBV, HIV.

Based on review of Gautam and Meena [12], surgery with negative surgical margins remained the primary treatment of intracranial LMS. Complete resection of the tumor was possible in majority of the reported cases, and it was associated with improved survival rate. Also, improving local control of the tumor has been reported by using radiation therapy after surgery [12]. In recent studies, Gamma Knife radiosurgery and stereotactic robotic cyber knife radiosurgery have been used for intracranial LMS [12,13].

There are also some reports about the use of chemotherapeutic agents for this disease because of high propensity for distant metastasis; however, results were inconsistent [12].

Based on a case report, a 19-year-old man who had no metastasis and normal serology finding underwent craniotomy with negative margins and then he received radiotherapy. No recurrences occurred after 18 months of follow-up [19].

Also, there was another case who was a 26-year-old man with primary intracranial LMS and no evidenced of metastasis. He had complete surgical resection and received post-operative radiotherapy with total dose of 61.8 Gy in 34 fractions. The patient declined chemotherapy. After 5 months of follow-up, liver and lung metastasis developed. The patient received liposomal doxorubicin with no response and died after 2 months [16].

Although most of the reported cases had surgery and post-operation radiotherapy, there is a report which the tumor was only removed by surgery. The was no recurrences despite the patient received no other treatment till the report of the paper [1].

There is a report of a man with a 4-year history of a temporo-occipital bump and disturbance with reading words. He had a sudden onset of headache in occipital region and evaluation revealed a temporal osteolytic mass lesion extending into the subcutaneous layer. After surgical removal of mass, local radiation therapy of 60 Gy was prescribed. But due to a left subdural hematoma and intrasylvian subarachnoid hemorrhage 3 months later and another temporal subcortical hemorrhage 2 months later, the patient died [3].

There is a report about late brain tumor recurrence by Maslehaty et al. [17] in 2016. They reported a 43-year-old man with the history of resected astrocytoma grade 1 in right cerebellar hemisphere 10 years before. He had another mass in right occipital lobe which was completely resected, and the pathology was LMS. They found no evidence of extracranial involvement. He received post-operative radiotherapy (50 Gy) and HDR brachytherapy (20 Gy). They reported 6 months of follow-up and there was no recurrence in the bed of tumor or distant metastasis [17].

A recent case report introduced a 23-year-old man with a history of EBV and HIV infection who had a lesion in the cavernous sinus. Only excisional biopsy was performed which was low grade LMS. Due to the mass location, complete resection could not be performed and the patient was treated with radiotherapy. In a short follow-up of 6 months after treatment, the patient had stable disease and was asymptomatic [5].

In our presented case, operation was performed with no residue and radiotherapy and systemic chemotherapy were prescribed. Although the reported cases in the literature had survival from 3 weeks to 44 months, the presented case was alive till the report and disease free for 34 months from the diagnosis and surgery. It might be due to the location of tumor which could be removed safely and also adjuvant radiotherapy and chemotherapy which decrease the incidence of local recurrence and systemic metastasis.

In conclusion, primary intracranial LMS is a very rare tumor. There is an association between these neoplasm and HIV and EBV in most of the cases. The diagnosis is based on histopathologic findings and IHC. Surgical resection is the main part of treatment. Prognosis of this neoplasm is poor due to the high propensity for local and distant recurrences. It seems that complete resection of tumor can help in local control of disease. In the review of literature and case reports, there were other treatment options too; such as radiotherapy and chemotherapy. Although the role of adjuvant chemotherapy is still on debate, some reports used it in the setting of distant metastasis.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

References

1. Torihashi K, Chin M, Yoshida K, Narumi O, Yamagata S. Primary intracranial leiomyosarcoma with intratumoral hemorrhage: case report and review of literature. World Neurosurg 2018;116:169-

73.
2. Li XL, Ren J, Niu RN, et al. Primary intracranial leiomyosarcoma in an immunocompetent patient: case report with emphasis on imaging features. Medicine (Baltimore) 2019;98:e15269.
3. Saito A, Ninomiya A, Ishida T, et al. Intractable repeated intracerebral hemorrhage due to primary dural leiomyosarcoma: case report and literature review. World Neurosurg 2019;122:116-22.
4. Bregy A, Lim J, Lohman R, et al. Primary leiomyosarcoma of the calvarium with intracranial extension: a case report. Indian J Surg Oncol 2020 Jul 1 [Epub]. https://doi.org/10.1007/s13193-020-01129-z.
5. Morales RL, Alvarez A, Norena MP, Torres F, Esguerra J. Low-grade leiomyosarcoma of the cavernous sinus in an HIV positive patient: case report. Cureus 2020;12:e6758.
6. Sadeh M, Chaudhry NS, Selner A, Behbahani M, Valyi-Nagy T, Atwal G. Intracranial leiomyoma associated with Epstein-Barr virus: a cerebellopontine angle mass presenting with trigeminal neuralgia. World Neurosurg 2020;141:284-90.
7. Niwa J, Hashi K, Minase T. Radiation induced intracranial leiomyosarcoma: its histopathological features. Acta Neurochir (Wien) 1996;138:1470-1.
8. Patel U, Patel N. Primary intracranial leiomyoma in renal transplant recipient. Saudi J Kidney Dis Transpl 2017;28:921-4.
9. Ritter AM, Amaker BH, Graham RS, Broaddus WC, Ward JD. Central nervous system leiomyosarcoma in patients with acquired immunodeficiency syndrome: report of two cases. J Neurosurg 2000;92:688-92.
10. Takei H, Powell S, Rivera A. Concurrent occurrence of primary intracranial Epstein-Barr virus-associated leiomyosarcoma and Hodgkin lymphoma in a young adult. J Neurosurg 2013;119:499-503.
11. Sivendran S, Vidal CI, Barginear MF. Primary intracranial leiomyosarcoma in an HIV-infected patient. Int J Clin Oncol 2011;16:63-6.
12. Gautam S, Meena RK. Primary intracranial leiomyosarcoma presenting with massive peritumoral edema and mass effect: Case report and literature review. Surg Neurol Int 2017;8:278.
13. Zhang H, Dong L, Huang Y, et al. Primary intracranial leiomyosarcoma: review of the literature and presentation of a case. Onkologie 2012;35:609-16.
14. Aeddula NR, Pathireddy S, Samaha T, Ukena T, Hosseinnezhad A. Primary intracranial leiomyosarcoma in an immunocompetent adult. J Clin Oncol 2011;29:e407-10.
15. Saito N, Aoki K, Hirai N, et al. Primary intracranial leiomyosarcoma of the cavernous sinus: case report. Austin J Med Oncol 2014;1:2.
16. Hussain S, Nanda A, Fowler M, Ampil FL, Burton GV. Primary intracranial leiomyosarcoma: report of a case and review of the literature. Sarcoma 2006;2006:52140.
17. Maslehaty H, Nabavi A, Mehdorn HM. Primary intracranial leiomyosarcoma: case report and principles for treatment. J Neurol Neuromed 2016;1:16-20.
18. Bejjani GK, Stopak B, Schwartz A, Santi R. Primary dural leiomyosarcoma in a patient infected with human immunodeficiency virus: case report. Neurosurgery 1999;44:199-202.
19. Alijani B, Yousefzade S, Aramnia A, Mesbah A. Primary intracranial leiomyosarcoma. Arch Iran Med 2013;16:606-7.
20. Brown HG, Burger PC, Olivi A, Sills AK, Barditch-Crovo PA, Lee RR. Intracranial leiomyosarcoma in a patient with AIDS. Neuroradiology 1999;41:35-9.

ROJ Radiation Oncology Journal

Case Report

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2020;38(4):287-290
https://doi.org/10.3857/roj.2020.00983

Management of grade 3 acute dermatitis with moist desquamation after adjuvant chest wall radiotherapy: a case report

Durim Delishaj[1], Romerai D'amico[1], Daniela Corvi[1], Giuseppe De Nobili[1], Alessandro Alghisi[1], Francesco Colangelo[2], Alessandra Cocchi[1], Fausto Declich[3], Carlo Pietro Soatti[1]

[1]*Department of Radiation Oncology, Alessandro Manzoni Hospital, Lecco, Italy*
[2]*Department of Radiation Oncology, University of Milano Bicocca, Milan, Italy*
[3]*Medical Physics Unit, Alessandro Manzoni Hospital, Lecco, Italy*

Received: November 21, 2020
Accepted: November 30, 2020

Correspondence:
Durim Delishaj
Department of Radiation Oncology, Alessandro Manzoni Hospital, Street Dell'Eremo 9/11, Lecco-23900, Lombardy, Italy
Tel: +39-341253540
Fax: +39-341489710
E-mail: delishaj@hotmail.com
ORCID:
https://orcid.org/0000-0002-1782-0852

We reported a successful case management of G3 skin acute dermatitis in a 32-year-old woman affected by locally advanced breast cancer underwent adjuvant chest wall irradiation. Skin acute toxicity with dry desquamation areas was treated daily with advanced dressing using physiological solution, oxygen therapy and applying hyaluronic acid gauze. At the end of radiotherapy treatment, G3 skin acute dermatitis with moist desquamation was observed, so the patient continued advanced wound dressing shifted to twice weekly with physiological solution, oxygen therapy and applying hydrocolloid dressing. The patient completed radiotherapy treatment without interruption and one month after treatment acute skin toxicity was resolved with pain relief. We suggest that advanced dressing with trained nursing staff is essential in this sub-set of patients due to guaranteed continuation of radiotherapy treatment, indispensable to ensure patient cure.

Keywords: Breast cancer, Radiotherapy, Dermatitis, Toxicity, Moist desquamation, Wound dressing

Introduction

Breast cancer is the most common female malignancy [1]. In the majority of patients, adjuvant radiation therapy, after conserving breast surgery or post-mastectomy, is indicate to improve locoregional control rate and overall survival [2]. External beam radiotherapy (EBRT) or high-dose rate brachytherapy are used for chest wall irradiation after mastectomy, re-irradiation or skin recurrences in patients with breast cancer. It is known that conventional radio-therapy treatment must be delivered daily and its interruption for long interval of time can influence efficacy and consequently locoregional control [3].

Adjuvant radiation therapy for breast cancer is generally well tolerated, however, acute skin toxicity is a common side effect that impacts quality of life especially in patients receiving either adjuvant chemotherapy [4]. Patients with breast cancer can develop severe acute radiation-induced skin reactions because their skin receives a relatively high dose as the tumor is close to the skin [4,5].

Most common symptoms of radiation induced dermatitis include irritation, pain, itching, peeling, and moist desquamation [5,6]. Moist desquamation (MD) occurs typically after a cumulative doses of 30 Gy as a result of destruction, sloughing of dermal layers and is characterized by serous fluid drainage and painful. MD often begins as small patches in skin folds and can progress to involve larger, confluent areas of irradiated skin.

Copyright © 2020 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

The risk of developing MD is highly variable and depending on radiation target as well as multiple patient and treatment factors. Typically the incidence rate are higher after post-mastectomy radiation therapy (with rates about 71%) compared to breast conservation (range, 11% to 47%) [7].

According to the Radiation Therapy Oncology Group (RTOG) and the Common Terminology Criteria for Adverse Events (CTCAE) scale, MD is classified as Grade 3 (G3) skin toxicity [8,9]. Some trials reported benefits using advanced dressing with significant lower levels of pain, burning, edema and management of MD in patients with higher grade acute skin toxicity [10-19].

We reported a successful case management of G3 skin acute dermatitis in a 32-year-old women affected by locally advanced breast cancer underwent adjuvant chest wall irradiation.

Case Report

In our center, about 300 patients with breast cancer receive adjuvant radiotherapy after surgery. We reported the case of a 32-year-old woman affected by locally advanced breast cancer. At the beginning of 2019 at self-examination, the patient noticed a lump on right breast with deformation of the nipple profile, for this reasons underwent clinical and imaging examination. The patient signed informed consent before starting radiotherapy treatment.

A breast magnetic resonance imaging (MRI) showed multifocal alterations of heteroplastic significance in lower quadrants of the right breast, characterized by increased gadolinium enhancement. Ultrasound guided fine-needle aspiration biopsy (FNAB) was positive for infiltrating ductal carcinoma. A computed tomography (CT) total body and bone scan had negative finding for distant metastasis. So, after multidisciplinary board evaluation, the patient underwent modified radical mastectomy with axillary lymph node dissection.

The histopathological examination confirmed multifocal infiltrating ductal carcinoma, G2, presence of perineural infiltration and focal endolymphatic invasion. The neoplasm infiltrated the striated muscle on the deep plane and coincided with margin for a maximum linear extension 1.3 mm, respectively. Eight axillary lymph nodes examined resulted free from cancer cells. The TNM histological stage resulted pT2(m)N0M0, G2, R1, estrogen receptor (ER) positive, progesterone receptor (PgR) positive, human epidermal growth factor receptor 2 (HER2) negative, and Ki-67 (40%).

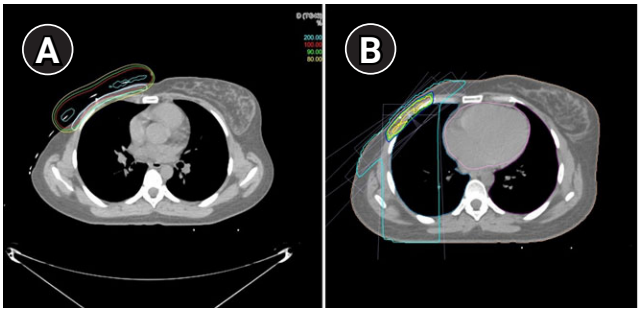


Fig. 1. Radiotherapy treatment planning using brachytherapy technique (A) and external beam radiation therapy technique (B).

After multidisciplinary breast board discussion and according to international breast cancer guidelines the patient was candidate to chemotherapy regimen with epirubicin-cyclophosphamide for four cycle and sequentially weekly paclitaxel for 12 cycle, aromatase inhibitors for 5 years and adjuvant chest wall radiotherapy.

From May 11, 2020 to June 12, 2020, the patient underwent chest wall irradiation with conventional fractionation at the dose of 46 Gy in 23 fractions using high-dose rate brachytherapy technique (Fig. 1A). A sequential boost of 14 Gy in 7 fractions was delivered using photon EBRT technique to positive margin, identified by the metal clips positioned during the surgery (Fig. 1B). Radiotherapy planning treatment was evaluated by radiation oncologist and all dose constraints for organs-at-risk were respected.

At the dose of 34 Gy, erythema G2 was observed which require to shift of local therapy from emollient cream to hyaluronic acid cream, commonly used for skin repair due to radiation damage. In addition, the patient reported mild pain controlled with non-steroidal anti-inflammatory drugs (NSAIDs).

At the dose of 46 Gy, G2 acute toxicity evolved with comparison of dry desquamation areas, so the patient needed advanced daily dressing with physiological solution, oxygen therapy and applying hyaluronic acid gauze with clinical benefit.

The patient completed radiotherapy treatment at the prescribed dose without interruption it. At the end of radiotherapy treatment skin acute toxicity evolved to G3 dermatitis with onset of MD at the irradiation area (Fig. 2A). For this reason, the patient continued advanced wound dressing shifted to twice weekly with physiological solution, oxygen therapy and applying hydrocolloid dressing.

Hydrocolloid dressing contains calcium alginate, which creates the ideal moist environment for the healing process of skin lesions by increasing perspiration based on the amount of exudate and keeping the lesion at constant temperature and humidity. One month after treatment G3 toxicity was resolved with pain relief and only topical emollient cream was applied (Fig. 2B).

Discussion

Adjuvant radiotherapy for breast cancer is well tolerated and radiation dermatitis is one of the most common side effects [1-3]. Typically, the incidence rate of radio-induced dermatitis is higher after

https://doi.org/10.3857/roj.2020.00983

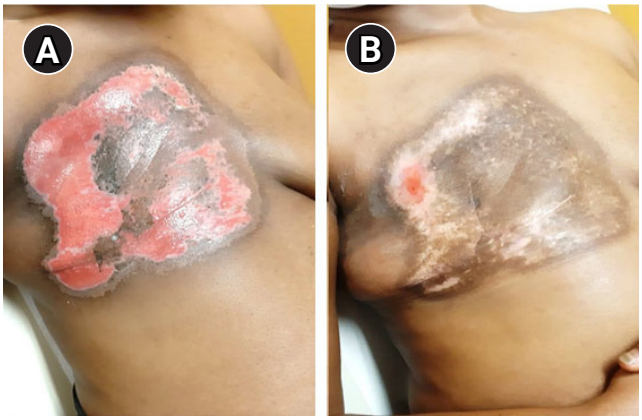


Fig. 2. Skin acute dermatitis (grade 3) during radiotherapy treatment (A) and resolution with advanced nursing dressing one month after treatment (B).

post-mastectomy radiation compared to breast conservation and usually consist in low-grade toxicity [4-6]. The use of new radiation techniques such as breast intensity-modulated radiation therapy seems to reduce the incidence of dermatitis in patients with breast cancer underwent adjuvant radiotherapy [16].

Emollient cream are widely used for the prevention and treatment of low grade acute dermatitis. Various studies analyzed the role topical therapy for the prevention and treatment of radiation induced dermatitis comparing different emollient cream, but failed to demonstrate the superiority of one over another [10-13]. Zhang et al. [12] published a meta-analysis of 20 reports of clinical trials using topical agents for prevention and treatment of radiodermatitis. In this analyses were included 3,098 patients and authors concluded that current topical agents do not prevent or treat radiation dermatitis effectively.

In the study of Nasser et al. [13], topical vitamin D ointment was not superior to aqua cream for prevention of radiation-induced dermatitis in women treated with adjuvant radiation for breast cancer. With the exception of corticosteroids, many different pharmacological topical treatments failed to consistently decrease skin reaction severity above standard care in breast cancer and head and neck cancer patients.

Bostrom et al. [15] in a double-blind randomized study showed that mometasone furoate, a potent corticosteroid cream, significantly reduces acute radiation dermatitis. Similar results were reported by other randomized clinical trials using mometasone furoate for the prevention of radiation induced dermatitis [16,17].

A randomized double-blinded phase 3 trial due clarify the clinical benefit of topical steroid for radiation dermatitis induced by high-dose irradiation with chemotherapy is ongoing (the study protocol of J-SUPPORT 1602) and the results will be soon available.

There are not a lot of data in literature regarding the management of G2/3 dermatitis after radiotherapy treatment and empirical treatment with antibiotics and corticosteroids is recommended, but often without immediate benefit and radiotherapy interruption is unavoidable due to prevent aggravation and complication of radiation induced dermatitis.

We reported a successful case management of G3 dermatitis using advanced dressing in a woman with breast cancer underwent chest wall adjuvant radiotherapy. The patient completed radiotherapy treatment without interruption despite comparison of G2/G3 dermatitis during radiotherapy treatment.

Some studies reported a clinical benefit using advanced dressing for G2/3 or highs radiation induced dermatitis [18-20]. In a phase I study, the use of topical epigallocatechin-3-gallate in patients with breast cancer receiving adjuvant radiotherapy appear to be effective in treating radiation dermatitis in this preliminary investigation [19]. Moreover, in a randomized intra-patient controlled clinical trial, Yan et al. [20] showed that Mepitel Film was superior to Biafine cream in reducing the severity of acute G3 radiation-induced skin reactions and moist desquamation incidence in head and neck patients.

In conclusion, we suggest advanced dressing with trained nursing staff for the management of G2/G3 radiation-induced dermatitis due to prevent aggravation of dermatitis and infectious complications. A trained nursing staff for an adequate management of G2/G3 radiation induced dermatitis is essential in this sub-set of patients due to guaranteed continuation of radiotherapy treatment, indispensable to ensure patient cure.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-32.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-41.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials.

Lancet 2011;378:1707-16.
4. Drost L, Li N, Vesprini D, et al. Prospective study of breast radiation dermatitis. Clin Breast Cancer 2018;18:e789-e795.
5. Butcher K, Williamson K. Management of erythema and skin preservation; advice for patients receiving radical radiotherapy to the breast: a systematic literature review. J Radiother Pract 2012; 11:44-54.
6. Wong RK, Bensadoun RJ, Boers-Doets CB, et al. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group. Support Care Cancer 2013;21:2933-48.
7. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-6.
8. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Internet]. Bethesda, MD: National Cancer Institute; 2017 [cited 2020 Dec 2]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.
9. Langberg M, Rotem C, Fenig E, Koren R, Ravid A. Vitamin D protects keratinocytes from deleterious effects of ionizing radiation. Br J Dermatol 2009;160:151-61.
10. Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. Clin Oncol (R Coll Radiol) 2005;17:478-84.
11. Sharp L, Finnila K, Johansson H, Abrahamsson M, Hatschek T, Bergenmar M. No differences between Calendula cream and aqueous cream in the prevention of acute radiation skin reactions: results from a randomised blinded trial. Eur J Oncol Nurs 2013; 17:429-35.
12. Zhang Y, Zhang S, Shao X. Topical agent therapy for prevention and treatment of radiodermatitis: a meta-analysis. Support Care Cancer 2013;21:1025-31.
13. Nasser NJ, Fenig S, Ravid A, et al. Vitamin D ointment for prevention of radiation dermatitis in breast cancer patients. NPJ Breast Cancer 2017;3:10.
14. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. J Clin Oncol 2004;22:1447-53.
15. Bostrom A, Lindman H, Swartling C, Berne B, Bergh J. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: results from a double-blind, randomized study. Radiother Oncol 2001;59:257-65.
16. Hindley A, Zain Z, Wood L, et al. Mometasone furoate cream reduces acute radiation dermatitis in patients receiving breast radiation therapy: results of a randomized trial. Int J Radiat Oncol Biol Phys 2014;90:748-55.
17. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008;26:2085-92.
18. Diggelmann KV, Zytkovicz AE, Tuaine JM, Bennett NC, Kelly LE, Herst PM. Mepilex Lite dressings for the management of radiation-induced erythema: a systematic inpatient controlled clinical trial. Br J Radiol. 2010;83:971-8.
19. Zhao H, Zhu W, Jia L, et al. Phase I study of topical epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy. Br J Radiol 2016;89:20150665.
20. Yan J, Yuan L, Wang J, et al. Mepitel Film is superior to Biafine cream in managing acute radiation-induced skin reactions in head and neck cancer patients: a randomised intra-patient controlled clinical trial. J Med Radiat Sci 2020;67:208-16.

Instructions for Authors

ROJ Radiation Oncology Journal

The Radiation Oncology Journal (ROJ) is a peer-reviewed publication of the Korean Society for Radiation Oncology. The ROJ is published quarterly on the last day of March, June, September, and December, one volume per year. Any physicians or researchers throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Articles in the following categories will be published: original articles, invited review articles, case reports, editorials, and letters to the Editor related to basic or clinical radiation oncology.

Manuscripts for submission to ROJ should be prepared according to the following instructions. ROJ follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/urm_main.html) commonly known as "the Vancouver style," if not otherwise described below.

1. RESEARCH AND PUBLICATION ETHICS

For the policies on the research and publication ethics not stated in this site, Good Publication Practice Guidelines for Medical Journals or Guidelines on Good Publication can be applied.

(1) Journal policies on authorship and contributorship

1) Authorship Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. 2) Originality and Duplicate Publication All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. Any part of the accepted manuscript should not be duplicated in any other scientific journal without the permission of the editorial board. If duplicate publication related to the papers of this journal is detected, the authors will be announced in the journal and their institutes will be informed, and there will also be penalties for the authors. 3) Secondary Publication It is possible to republish manuscripts if the manuscripts satisfy the conditions of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. ROJ maintains a zero-tolerance policy when addressing allegations of plagiarism, duplicate publication (self-publication), data falsification, and scientific misconduct. Articles will be retracted if ethics violations are substantiated. Plagiarism is defined by the World Association for Medical Editors (WAME) as the "use of others' published and unpublished ideas or words (or other intellectual property) without attribution or permission, and presenting them as new and original rather than derived from an existing source." ROJ participates in the CrossCheck/iThenticate program to investigate incidents of possible plagiarism. Manipulating data through fabrication, omission, or intentional distortion is unacceptable. Authors should be prepared to provide original data to editors if there is a question of authenticity. Claims of scientific misconduct are investigated and addressed, guided by the Committee of Publication Ethics (COPE) Code of Conduct.

(2) Statement of Informed Consent

Copies of written informed consent and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

(3) Statement of Human and Animal Rights

All human investigations must be conducted according to the principles expressed in the Declaration of Helsinki. All studies involving animals must state that the guidelines for the use and care of laboratory animals of the authors' institution, or any national law, were followed.

(4) How the journal will handle complaints and appeals

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of ROJ will discuss the suspected cases and reach a decision. ROJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed

(5) Journal policies on conflicts of interest/competing interests

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappro-

priately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having great a potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and background for the completed research. The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data.

(6) Journal policies on data sharing and reproducibility

1) Open data policy For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data or waiver of data sharing, authors should contact the editorial office. 2) Clinical data sharing policy This journal follows the data sharing policy described in "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors" (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing statement as described below. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record. All of the authors of research articles that deal with interventional clinical trials must submit data sharing plan. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

(7) Journal's policy on ethical oversight

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

(8) Journal's policy on intellectual property

All published papers become the permanent property of the Korean Society for Radiation Oncology. Copyrights of all published materials are owned by the Korean Society for Radiation Oncology.

(9) Journal's options for post-publication discussions and corrections

The post-publication discussion is available through letter to editor. If any readers have a concern on any articles published, they can submit letter to editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

2. ELECTRONIC SUBMISSION OF MANUSCRIPT

Manuscript submission is only available through the online submission site at http://submit.e-roj.org. Submission instructions are available at the website. All articles submitted to the ROJ must comply with these instructions. Failure to do so will result in return of the manuscript and possible delay in publication. For assistance please contact us via E-mail (rojeditor@gmail.com), telephone (+82-2-3410-2612).

3. PEER REVIEW PROCESS

The acceptance criteria for all papers are based on the quality and originality of the research and its clinical and scientific significance. Original Articles are generally reviewed at least by two peer reviewers. The Editor-in-Chief is responsible for final decisions regarding the acceptance if a peer-reviewed paper. An initial decision will normally be made within 4 weeks of receipt of a manuscript, and the reviewers' comments are sent to the corresponding authors by E-mail. Revised manuscripts must be submitted online by the corresponding author. The corresponding author must indicate the alterations that have been

made in response to the referees' comments item by item. Failure to resubmit the revised manuscript within 12 weeks of the editorial decision is regarded as a withdrawal.

4. MANUSCRIPT PREPARATION

(1) General Guideline

Authors are required to submit their manuscripts after reading the following instructions. Any manuscript that does not conform to the following requirements will be considered inappropriate and may be returned. When a manuscript is received for consideration, the editors assume that no similar paper has been or will be submitted for publication elsewhere. The main document with manuscript text and tables should be prepared with an MS-word programs.

- The manuscript should be written in 11-point font with double-line spacing on A4 sized (21.0×29.7 cm) paper with 25 mm margins on the top, bottom, right and left.
- All manuscript pages are to be numbered at the middle of bottom consecutively.

(2) Language

Manuscripts must be written succinctly in clear, grammatical English. All manuscripts originating from non-English speaking countries must be revised by a professional linguistic reviewer. Medical terminology should be written based on the most recent edition of Dorland's Illustrated Medical Dictionary or the most recent edition of English-Korean Korean-English Medical Terminology, published by the Korean Medical Association. The use of acronyms and abbreviations is discouraged and should be kept to a minimum. When used, they are to be defined where first used, followed by the acronym or abbreviation in parentheses. Drug and chemical names should be stated in standard chemical or generic nomenclature. Units of measure should be presented according to the SI units (e.g., Gy, Sv, Bq, m, kg, L).

(3) Reporting Guidelines for Specific Study Designs

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

ORIGINAL ARTICLES

Original articles are reports of basic or clinical investigations. The manuscript for an original article should be organized on a separate page in the following sequence: title page, abstract and keywords, text (introduction, materials and methods, results, discussion and conclusion), conflicts of interest, acknowledgments (if necessary), references, tables, and figure legends.

1) Title page

Title Page should carry the following information.

- The title should be short, informative, and contain the major key words (no more than 15 words). It is not necessary to lead with expressions like "clinical research on -" or "the study on -."
- Each author's name (first name, middle name, and surname) followed by the highest academic degree (e.g., Gil Dong Hong, MD).
- The name of department (s) and institution (s) where the work was conducted. If the authors' affiliation is different, indicate individual departments and institutions by inserting a superscript letter immediately after the author's name, and the same letter in front of the appropriate institution.
- Running title of fewer than 60 characters.
- Source(s) of support in the form of grants, equipment, drugs, or all of these.
- Complete mailing address, telephone, and E-mail for correspondence and reprints.

2) Abstract and Keywords

The abstract should be no more than 250 words, and describe concisely, in a paragraph, Purpose, Materials and Methods, Results, and Conclusion. Up to six keywords should be listed below the abstract. For selecting keywords, refer to the Medical Subject Headings; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

3) Text

Text should be arranged in following order: Introduction, Materials and Methods, Results, Discussion and Conclusion. Materials and Methods section should include sufficient details of the research design, subjects, and methods. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and meta-analyses	http://www.prisma-statement.org
STROBE	Observational studies inepidemiology	http://www.prisma-statement.org
MOOSE	Observational studies in epidemiology	http://www.strobe-statement.org

replicated by others. The sources of special chemicals or reagents should be given along with the source location (name of the company, city, state/province, and country). If needed, information on the institutional review board/ethics committee approval or waiver and informed consent are included. Methods of statistical analysis and criteria for statistical significance should be described.

4) Conflicts of Interest

All potential conflicts of interest must be stated within the text of the manuscript, under this heading. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products. Other areas of real or perceived conflict of interest could include receiving honoraria or consulting fees or receiving grants or funds from such corporations or individuals representing such corporations. Please state "None" if no conflicts exist.

5) Acknowledgments

If necessary, persons who have made substantial contributions, but who have not met the criteria for authorship, are acknowledged here. All sources of funding applicable to the study should be stated here explicitly.

6) References

In the text, references should be cited with Arabic numerals in brackets, numbered in the order cited. In the references section, the references should be numbered in order of appearance in the text and listed in English. List all authors if there are less than or equal to six authors. List the first three authors followed by "et al." if there are more than three authors. If an article has been published online, but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied. Journal titles should be abbreviated in the style used in Medline. Other types of references not described below should follow Citing Medicine: The NLM Style Guide for Authors, Editors, and Publishers.

Journal articles:

1. Yu JI, Park HC, Choi DH, et al. Prospective phase II trial of regional hyperthermia and whole liver irradiation for numerous chemorefractory liver metastases from colorectal cancer. Radiat Oncol J 2016;34:34-44.
2. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. Int J Radiat Oncol Biol Phys. 2011 Mar 4 [Epub]. http://dx.doi.org/10.1016/j.ijrobp.2010.11.048.

Book:

3. Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG. Abeloff's clinical oncology. 4th ed. Philadelphia, PA: Churchill Livingstone; 2008.
4. Jain RK, Kozak KR. Molecular pathophysiology of tumors. In: Halperin EC, Perez CA, Brady LW, editors. Perez and Brady's principles and practice of radiation oncology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 126-41.

Conference paper:

5. Medin PM, Foster RD, von der Kogel, Sayre J, Solberg TD. Spinal cord tolerance to reirradiation with radiosurgery: a swine model. In: 52th ASTRO Annual Meeting; 2010 Oct 31 - Nov 11; San Diego, CA, USA. Farifax, VA: ASTRO; 2010.

Online sources:

6. American Cancer Society. Cancer facts & figures [Internet]. Atlanta, GA: American Cancer Society; c2011 [cited 2011 Feb 20]. Available from: http://www.cancer.org/Research/CancerFactsFigures/index.
7. National Cancer Information Center. Cancer incidence [Internet]. Goyang (KR): National Cancer Information Center; c2011 [cited 2011 Oct 20]. Available from: http://www.cancer.go.kr/cms/statics.

7) Tables

Each table should be typed in the separate sheet. The title of the table should be on top placed and the first letter of all word (except articles, conjunctions, prepositions) should be capitalized. Tables are numbered in order of citation in the text. Lower case letters in superscripts a), b), c) ... should be used for special remarks. Within a table, if a non-standard abbreviation is used or description may be necessary, then list them under annotation below. The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis.

8) Figures

Upload each figure as a separate image file. The figure images should be provided in PowerPoint file, TIFF, JPEG, GIF or EPS format with high resolution (preferably 300 dpi for figures and 600 dpi for line art and graph). The figures should be sized to column width (8.5 cm or 17.5 cm). If figures are not original, author must contact each publisher to request permission and this should be remarked on the footnote the figure. Figures should be numbered, using Arabic numerals, in the or-

der in which they are cited. All figures should be cited in the text (e.g., Fig. 1, Fig. 1A-C, Figs. 1 and 2). In the case of multiple prints bearing the same number, use capital letters after the numerals to indicate the correct order (e.g., Fig. 1A, Fig. 1B). A figure legend should be in English and a one-sentence description rather than a phrase or a paragraph. Capitalize the first letter of the first word. A legend for each light microscopic photograph should include name of stain and magnification. Electron microscopic photograph should have an internal scale marker.

REVIEWS

Reviews should be comprehensive analyses of specific topics. They are organized as follows: title page, abstract and keywords, introduction, body text, conclusion, conflicts of interest, acknowledgments (if necessary), references, tables, and figure legends. Upload each figure as a separate image file. There should be an unstructured abstract equal to or less than 200 words. References should be obviously related to documents and should not exceed 50.

CASE REPORTS

Case reports will be published only in exceptional circumstances, when they illustrate a rare occurrence of clinical importance. The manuscript for a case report should be organized in the following sequence: title page, abstract and keywords, introduction, case report(s), discussion, conflicts of interest, acknowledgments (if necessary), references, tables, and figure legends. Upload each figure as a separate image file. The abstract should be unstructured and its length should not exceed 150 words. References should be obviously related to documents and should not exceed 20. It is not necessary to use the word "introduction."

EDITORIAL

Editorials should be commentaries on articles published recently in the journal. Editorial topics could include active areas of research, fresh insights, and debates. Editorials should be no more than four to five pages in length including references, tables, and figures.

LETTERS TO THE EDITOR

Letters to the Editor should include brief constructive comments that concern previously published papers. Letters to the Editor should be no more two pages. It should have maximum 5 references, 1 table and 1 figure. Letters could be edited by the Editorial Board. Responses by the author of the subject paper may be provided in the same issue or next issue of the Journal

5. COMMUNICATIONS TO THE PUBLISHER

We invite inquiries to the editorial office at any time during the editorial process. For all matters concerning presubmission, editorial policies, procedures, business inquiries, subscription information, orders, or changes of address, please contact editorial office.

Editorial Committee Office
The Korean Society for Radiation Oncology
Department of Radiation Oncology, Samsung Medical Center, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-2612
E-mail: rojeditor@gmail.com, homepage: http://e-roj.org

6. ADDITIONAL INFORMATION

(1) Copyright

All published papers become the permanent property of The Korean Society for Radiation Oncology. Upon acceptance of the manuscript, the authors will be required to sign a statement confirming that the manuscript contains no material the publication of which violates any copyright or other personal or proprietary right of any person or entity.

(2) Page Proofs

Corresponding authors are provided with page proofs and are asked to carefully review them for data and typesetting errors. When proofs are available, the corresponding author will receive a notification. Corrections to proofs must be returned via e-mail within 48 hours. Publication may be delayed if proofs are not returned by the publisher's deadline.

(3) Charges

There are no charges for submission and publication.

NOTICE: These recently revised instructions for authors will be applied beginning with the June 2016 issue.

Research and Publication Ethics

ROJ Radiation Oncology Journal

For the policies on the research and publication ethics not stated in this site, Good Publication Practice Guidelines for Medical Journals or Guidelines on Good Publication can be applied.

1. Journal policies on authorship and contributorship

1) Authorship

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions.

2) Originality and Duplicate Publication

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. Any part of the accepted manuscript should not be duplicated in any other scientific journal without the permission of the editorial board. If duplicate publication related to the papers of this journal is detected, the authors will be announced in the journal and their institutes will be informed, and there will also be penalties for the authors.

3) Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. ROJ maintains a zero-tolerance policy when addressing allegations of plagiarism, duplicate publication (self-publication), data falsification, and scientific misconduct. Articles will be retracted if ethics violations are substantiated. Plagiarism is defined by the World Association for Medical Editors (WAME) as the "use of others' published and unpublished ideas or words (or other intellectual property) without attribution or permission, and presenting them as new and original rather than derived from an existing source." ROJ participates in the CrossCheck/iThenticate program to investigate incidents of possible plagiarism. Manipulating data through fabrication, omission, or intentional distortion is unacceptable. Authors should be prepared to provide original data to editors if there is a question of authenticity. Claims of scientific misconduct are investigated and addressed, guided by the Committee of Publication Ethics (COPE) Code of Conduct.

2. Statement of Informed Consent

Copies of written informed consent and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

3. Statement of Human and Animal Rights

All human investigations must be conducted according to the principles expressed in the Declaration of Helsinki. All studies involving animals must state that the guidelines for the use and care of laboratory animals of the authors' institution, or any national law, were followed.

4. How the journal will handle complaints and appeals

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of ROJ will discuss the suspected cases and reach a decision. ROJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

5. Journal policies on conflicts of interest/competing interests

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing

loyalties. These relationships vary from being negligible to having great a potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and background for the completed research. The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data.

6. Journal policies on data sharing and reproducibility

1) Open data policy

For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data or waiver of data sharing, authors should contact the editorial office.

2) Clinical data sharing policy

This journal follows the data sharing policy described in "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors" (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing statement as described below. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record. All of the authors of research articles that deal with interventional clinical trials must submit data sharing plan. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

7. Journal's policy on ethical oversight

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

8. Journal's policy on intellectual property

All published papers become the permanent property of the Korean Society for Radiation Oncology. Copyrights of all published materials are owned by the Korean Society for Radiation Oncology.

9. Journal's options for post-publication discussions and corrections

The post-publication discussion is available through letter to editor. If any readers have a concern on any articles published, they can submit letter to editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

Checklist

ROJ Radiation Oncology Journal

- ☐ Copyright transfer form has been signed by all authors.
- ☐ Ethics disclosure form has been signed by corresponding author.
- ☐ The manuscript shall be written by Microsoft Office Word or HWP processing programs.
- ☐ A title page including author details and a manuscript without author details of the original file of the article should be submitted separately.
- ☐ The original file of the article should not include the affiliations and names of the authors.
- ☐ Standard abbreviations are defined in a key at their first appearance in the manuscript, and are consistent throughout the text.
- ☐ Generic names are used for all drugs. Trade names are avoided.
- ☐ Normal laboratory values are provided in parentheses when first used.
- ☐ Research or project support/funding is noted in cover letter.
- ☐ Internal review board approval of study is indicated in cover letter.
- ☐ References are accurate, complete and in numerical order as they appear in the text, only the first 3 authors are listed.
- ☐ No more than 50 references are cited in review article.
- ☐ No more than 55 references are cited in original article.
- ☐ No more than 20 references are cited in case report.
- ☐ A corresponding author and complete address, telephone number and e-mail address are provided in cover letter.
- ☐ Written permission from publishers to reproduce or adapt previously published illustrations or tables is included.
- ☐ Informed consent forms for identifiable patient descriptions, photographs and pedigrees are included.

Copyright Transfer Form

ROJ Radiation Oncology Journal

This form applies to manuscripts submitted for the possible publication

Manuscript Title: _____

Date (M/D/Y): _____

Manuscripts will not be processed until the Radiation Oncology Journal Editorial Office has received this signed form. Please upload the completed form when you submit a manuscript on the E-Submission website (submit.e-roj.org).

The copyright to this article is transferred to the Radiation Oncology Journal (ROJ) effective if and when the article titled above is accepted for publication. If the article has more than two authors, each author must individually transfer his or her right in the article to the ROJ by signing this form. If the article is not published in the ROJ, this form is void and will not take effect. If it is signed and the article is published, the copyright transfer covers the exclusive right to reproduce and distribute the article, including reprints, translation, photographic reproduction, microfilm, electronic form (offline, online) or any other reproductions of similar feature.An author or authors may store it in his or her archive an author-made version of his/her article on his/her own website and his/her affiliated institution's depository library, including his/her final version; however he/she may not use the ROJ's PDF version which is posted on its own website. Provided permission is given to the author/authors by ROJ, he/she may only post his/her version of the article and a link to the original source of publication is inserted to the published article on the ROJ's website.Please use the exact and correct DOI for the article to ensure appropriate linking between sites. Articles listed on the ROJ's website are indexed, abstracted, and referenced by many indexing services and consortia such as SCIE, EMBASE, Google Scholar and KMCI.Each author guarantees that this contribution is original and that he/she has full responsibility to make this grant. The author signs for and accepts full responsibility for releasing this content. The author should declare that, to the best of his/her knowledge and belief, this manuscript does not infringe on the copyright or other proprietary rights of any third party. The author should understand that his/her submission of this manuscript does not guarantee publication in the ROJ. If there are multiple authors, names will appear in the ROJ in the order in which you listed them during the online submission and on this sheet. Therefore, please be sure to list names according the order you want to see in the final version. Each author should sign on the following, as appropriate.

Name (Print)	Signature

보건의료전문가용

IMFINZI™
durvalumab
Injection for Intravenous Use 50 mg/mL

THE FIRST AND ONLY APPROVED

THE STANDARD OF CARE FOR STAGE III UNRESECTABLE NSCLC

Following CCRT with PD-L1>= 1%[1]

임핀지 2020년 4월 1일 보험급여 적용

PD-L1 발현 양성(발현 비율 ≧ 1%)이면서 백금 기반 동시적 항암화학방사선요법 2주기 이상 투여 후 질병진행이 없는 안정병변 이상의 절제 불가능한 국소 진행성(stage III)비소세포폐암 환자로 CCRT 치료 종료 이후 42일 내에 투여하는 경우[1]

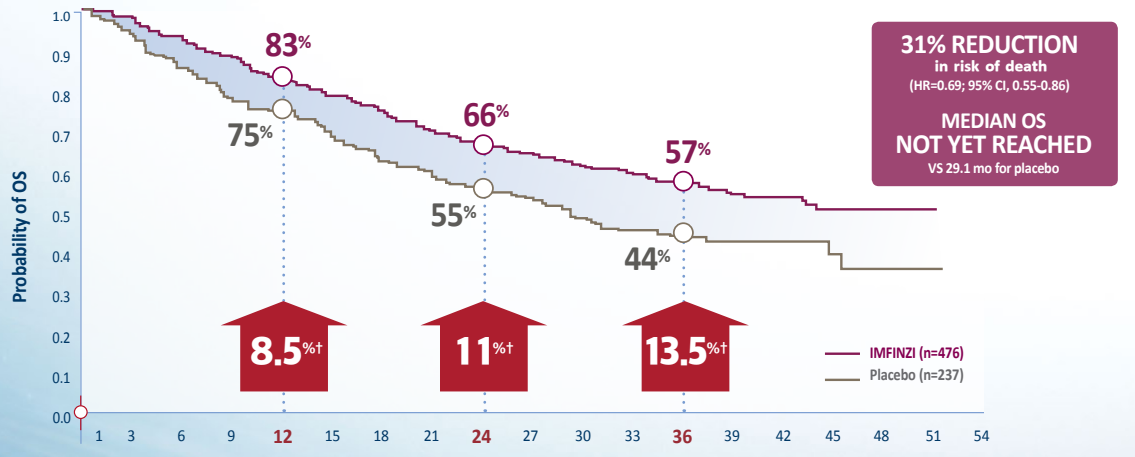
※ 급여 인정 기간은 최대 12개월로 함

※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함.

- PD-L1 발현 1% 이상
- CCRT 이후 42일 이내
- 급여인정기간 1년
- 이후 고식적 요법의 면역관문억제제 투여가능

PACIFIC 연구에서 임핀지 치료군의 3년 전체생존율(OS rate)은 57%로 장기적인 생존 개선 이점을 확인하였습니다.[2]

3-year overall survival update[2]



As of January 31, 2019 (data cutoff)

Number of patients at risk

IMFINZI	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0

† Durvalumab OS rate differences compared to Placebo

REFERENCE **1.** 보건복지부 고시 제 2020-61호, 건강보험심사평가원 공고 제 2020-81호, 시행일: 2020.04.01 **2.** Gray JE et al. Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC-Update from PACIFIC Journal of Thoracic Oncology, S1556-0864(19)33529-4

STUDY DESIGN_ The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage III, unresectable NSCLC, with a WHO performance score of 0 or 1. Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy without progression, and the last radiation dose was 1-42 days before randomization. Tumor tissue collection was not a prerequisite for inclusion in PACIFIC and enrollment was notrestricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every two weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. Randomization was stratified by age of the patient (<65 years vs ≥65 years), sex, and smoking history (current or former vs never smoked). The primary end points were progression free survival (as assessed by blinded independent central review) and overall survival.

PRESCRIBING INFORMATION

[효능·효과]백금 기반 동시적 항암화학방사선요법 이후 질병이 진행되지 않은 절제불가능한 국소 진행성 비소세포폐암 환자의 치료**[용법·용량]** 권장 용량은 이 약 10mg/kg을 2주 간격으로 60분에 걸쳐 정맥 점적 주입하는 것이다. 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다.용량 증가나 감소는 권장되지 않는다. 개인의 안전성과 내약성에 따라 투여 보류 또는 중단이 필요할 수 있다. 면역 매개 이상사례의 관리에 대한 가이드라인은 다음과 같다. 추가 모니터링 및 평가 정보는 사용상의 주의사항을 참조한다. **[이 약의 용법 조절 및 관리 권장 사항]**

이상사례	중증도 (CTCAE v4.0기)	용법 조절	코르티코스테로이드 요법 및 그 외
면역 매개 폐렴/ 간질성 폐질환	2등급	투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	1~4 mg/kg/일의 프레드니손 또는 동가량의 투여 후 용량 감량
면역 매개 간염	2등급이고, 혈청 아미노전이효소 (ALT) 또는 아스파르테이트 아미노전이효소 (AST)가 정상상한치의 3~5배를 초과하거나 총 빌리루빈이 정상상한치의 1.5~3배를 초과	투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3등급이고, ALT 또는 AST가 정상상한치의 5배 초과, 8배 이하 또는 총 빌리루빈이 정상상한치의 3배 초과 5배 이하		
	3등급이고, ALT 또는 AST가 정상상한치의 8배를 초과 또는 총 빌리루빈이 정상상한치의 3배를 초과	투여 중단	
	다른 유의한 원인과 ALT 또는 AST가 정상상한치의 3배를 초과하고 총 빌리루빈이 정상상한치의 2배를 초과하는 경우		
면역 매개 대장염 또는 설사	2등급	투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	
면역 매개 내분비병: 갑상선 기능 장전증	2~4등급	갑상선으로 안정할 때까지 투여 보류	대증적 관리
면역 매개 내분비병: 갑상선 기능 저하증	2~4등급	변경하지 않음	임상 지시대로 갑상선 호르몬 대체 개시
면역 매개 내분비병: 부신 기능 부전, 뇌하수체염/뇌하수체 저하증	2~4등급	임상적으로 안정할 때까지 투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량 및 임상 지시대로 호르몬 대체 개시
면역 매개 내분비병: 제1형 당뇨병	2~4등급	임상적으로 안정할 때까지 투여 보류	임상적 지침로 인슐린 치료 개시
면역 매개 신장염	2등급이고, 혈청 크레아티닌이 정상상한치 또는 기저치의 1.5~3배를 초과	투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3등급이고, 혈청 크레아티닌이 기저치의 3배를 초과 또는 정상상한치의 3~6배를 초과하거나 4등급이고 혈청 크레아티닌이 정상상한치의 6배를 초과	투여 중단	
면역 매개 발진 또는 피부염	2등급이고 1주 이상 초과	투여 보류	1~2 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3등급	투여 중단	
	4등급	투여 중단	
면역 매개 심근염	2등급	투여 보류	2~4 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	3 또는 4등급 또는 재발 생검을 동반한 모든 등급	투여 중단	
면역 매개 근육염/다발근육염	2등급 또는 3등급	투여 보류	2~4 mg/kg/일의 프레드니손 또는 동가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
주입 관련 반응	1 또는 2등급	주입을 중단하거나 느리게 주입	증속 조절 없이의 예방을 위해 사전 약물 치료를 고려할 수 있음
	3 또는 4등급	투여 중단	

*이상사례 표준 용어기준 (Common Terminology Criteria for Adverse Events; CTCAE), 버전 4.03

†약화되거나 개선이 없다면, 코르티코스테로이드의 용량 증가 및/또는 다른 전신 면역 억제제 사용을 고려한다. 1등급 이하로 개선되면, 코르티코스테로이드의 감량을 시작하여 최소 1개월 간 지속하여야 한다. 투여 보류 후, 1등급 이하로 개선되고 코르티코스테로이드 용량이 일일 10mg 프레드니손 또는 동가량 이하로 감소되었을 경우, 1주후 이내에서 이 약의 투여를 다시 시작할 수 있다. 3등급 또는 4등급(중증 또는 생명을 위협하는) 이상사례 재발의 경우 이 약을 중단한다.

‡ 코르티코스테로이드 투여에도 불구하고 3-5일 이내에 개선이 없다면, 신속히 추가적인 면역억제 치료를 시작한다. 회복(0등급)하면, 코르티코스테로이드의 감량을 시작하여 하고 최소 1개월 간 지속한 후 임상적 판단에 따라 이 약의 투여를 다시 시작할 수 있다.

§ 이상사례가 30일 이내에 1등급 이하로 회복되지 않거나 조절기 기능부전의 징후가 있는 경우에는 이 약 투여를 중단한다. 의심되는 면역 매개 이상사례에 대해, 병인 확인 또는 대체 병인을 배제하기 위한 적절한 평가가 수행되어야 한다. 위의 표에 포함되지 않은 기타 면역 매개 이상사례에 대해, 4등급 이상사례의 경우 이 약의 투여를 중단하여야 한다. 임상적 판단으로 투여 중단이 필요한 경우 외에는 3등급 면역 매개 이상사례의 경우 이 약의 투여 보류를 고려하여야 한다. 전신 코르티코스테로이드 요법을 고려하여야 한다. 바-면역 매개 이상사례에 대해, 2등급과 3등급 이상사례의 경우 1등급 이하가 될 때까지 이 약의 투여를 보류한다. 4등급 이상사례의 경우 이 약 투여를 중단한다 (예외적으로 4등급 실험실 검사수치 이상의 경우, 수반된 임상 징후 및 임상적 판단에 근거하여 투여 중단을 결정한다).

이 약은 경등도 간질환 환자에서는 용량 조정이 권장되지 않으며, 중등도 또는 중증 간질환 환자에서는 연구되지 않았다.

투여방법- 투여 전 이 약은필요한 희석액 지시 사항은 사용상의 주의사항 13. 취급상의 주의사항을 참고한다. 멸균된 저 단백질 결합 0.2 또는 0.22 미이크로미터 인라인 필터(in-line filter)를 포함하는 정맥 주사 라인을 통해 60분에 걸쳐 주사액을 정맥 내 투여한다. 같은 주입 라인으로 다른 약물을 동시 투여하지 않는다. 사용하고 남은 약물이나 물품은 관련 규정에 따라 폐기되어야 한다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 이 약의 주성분 또는 첨가제에 과민증 병력이 있는 환자 2. 다음 환자에는 신중히 투여할 것 자가면역질환 또는 자가면역질환 병력이 있는 환자 3. 약물이상반응 1) 임상시험에서 보고된 이상사례 PACIFIC 연구 (475명)에서 국소 진행성 절제불가능한 비소세포폐암 환자로 이 연구 시작 전 1~42일 내에 2주기 이상의 항암화학방사선요법을 완료한 환자들을 대상으로 이 약(10 mg/kg)의 안전성이 평가되었다. 이 환자 집단에서 가장 흔한 이상사례는 기침 (40.2%, 위약군 30.3%), 상부 호흡기 감염 (26.1%, 위약군 11.5%) 및 발진 (21.7%, 위약군 12.0%)이었다. 3 또는 4등급 이상사례의 발생률은 이 약 투여군에서 12.9%, 위약군에서 9.8%이었다. 가장 흔한 3 또는 4등급 이상사례는 폐렴 (6.5%, 위약군 5.6%)이었다. 이 약 투여군의 0.2% 및 위약군의 5.6%에서 이상사례로 인해 투약을 중단하였다. 이 약의 투약 중단으로 이어진 가장 흔한 이상사례는 이 약 투여군 1.2%) 및 위약군 11.1%의 환자에서 발생하였다. 가장 흔한 중대한 약물이상반응은 2% 이상의 환자에서 보고된 간질폐렴과 폐렴이었다. 치명적인 간질폐렴과 치명적인 폐렴은 이 약 투여군과 위약군 간에 유사하게 1% 미만의 환자에서 보고되었다. 이상사례는 MedDRA의 기관계 분류에 따라 기재되었다. 각 기관계 분류에서, 이상사례는 빈도가 높은 순으로 표기되었다. 각 빈도 군에서, 이상사례는 중증도가 높은 순으로 표기되었다. 또한, 각 이상사례의 해당 빈도 분류는 CIOMS III 협의에 따르며 다음과 같이 정의된다: 매우 흔하게 (≥1/10), 흔하게 (≥1/100에서 <1/10), 흔하지 않게 (≥1/1,000에서 <1/100), 드물게 (≥1/10,000에서 <1/1,000), 매우 드물게 (<1/10,000), 빈도 불명. 즉 이용 가능한 자료로부터 추정될 수 없음. **[저장방법]** 일봉용기, 2-8℃에서 저장하여 보관 **[포장단위]** 2.4mL x 1 바이알 / 박스, 10mL x 1 바이알 / 박스. ※ 한국 구입시 사용기한이 경과되었거나 변질, 변색 또는 오손된 제품인 경우에는 구입자를 통하여 교환하여 드리며, 공정거래위원회 고시 "소비자분쟁해결기준"에 의거 소비자의 정당한 피해는 보상하며 드림니다. 의약품 부작용 발생 시 한국의약품안전관리원에 피해구제를 신청하실 수 있습니다. 문헌개정연월일: 2019년 11월 5일 제조자(위탁 제조): AstraZeneca AB, Neuhofstrasse 34, 6340 Baar, 스위스 제조자 (최종완역제조): AstraZeneca Pharmaceuticals Limited Partnership, Frederick Manufacturing Center (FMC), 633 Research Court, Frederick, MD 21703, 미국 제조자 (충전: Catalent Indiana LLC, 1300 South Patterson Drive, Bloomington, Indiana, IN 47403, 미국 제조자 (2차포장): AstraZeneca AB, Forskargatan 18, SE-151 85 Södertälje, 스웨덴 수입사·입자: 한국아스트라제네카 서울시 강남구 영동대로517 아셈타워 21층, 전화 02-2188-0800

***보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다**: aFZ20191106

KR-5835 | Exp. 20220408

한국아스트라제네카 서울시 강남구 영동대로 517 아셈타워 21층 전화: (02) 2188-0800 팩스: (02) 2188-0852

AstraZeneca