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## 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.

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Review Article

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# The effect of radiotherapy on rectal cancer: a histopathological appraisal and prognostic indicators

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The management of rectal cancer is a major undertaking. There are currently multiple treatment modalities with variable degrees of complications. Radiotherapy (RT) is one of the more frequently used modalities either on its own or more frequently with chemotherapy mostly before the definitive surgery. The outcome of RT is unpredictable. RT has its serious side effects and there are no guarantees of its usefulness in all patients. This article outlines the effect of RT on the tumor, reviews the various staging systems of responses to RT and present recent evidence of which case is less responsive to such treatments to avoid unnecessary complications.

**Keywords:** Rectal cancer, Therapeutic oncology, Clinical pathology, MicroRNAs, Regression, Chemoradiotherapy

## Introduction

Rectal cancer is one of the more frequent human malignancies accounting for 3.9% of all new cancer cases causing 3.2% of all cancer-related deaths globally in 2018 [1]. The survival of the disease increased in the last years reaching an overall 5-year rate of 67% [2]. This could be related to the medical advances in rectal cancer treatment, increased awareness and screening [3].

Surgery is still the mainstay of treatment for rectal cancer since the introduction of abdomino-perineal resection techniques in 1908 [4]. Since then advances progressed the surgical platform and total mesorectal excision (TME) became the standard surgical approach ever since its introduction by Heald and Ryall [5] in 1982.

Neoadjuvant and adjuvant therapies have been repeatedly tested in many trials to improve the outcomes of rectal cancer patients in terms of local recurrence and survival. The addition of radiotherapy (RT), in addition to the improvement in surgical techniques, demonstrated improvement in local recurrence [6,7]. Despite that, other studies reported that around one-fifth of the cases will have no response to RT. Other workers reported that the contribution of neoadjuvant RT to pathological complete response in terms of survival was of limited or minimal benefit [8].

In view of the above changes, the real challenge in rectal cancer treatment is to identify patients who would fully benefit from the new treatment protocols which involve RT. The aim of this article is to present the different histological systems used to classify the response rate of the patients and to discuss the different types of biomarkers used to predict of the response of patients to RT/chemoradiotherapy (CRT).

## RT Mechanism of Action

Oxidative stress damage is extensive in cells exposed to ionising radiation. This damage mainly targets nuclear DNA through inhib-

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iting DNA transcription in both direct and indirect pathways [9]. DNA damage is caused by the direct targeting nuclear chromatin. This damage will find the way through generating intra- and inter-strand chromosomal cross linkages along with breaks and mutations of DNA material. Direct damage to plasma membrane happens by disrupting both electrical gradient and the rigidity of the two layers of phospholipids membranes affecting the cell integrity. The indirect pathway is through free radicals from the ionisation of $H_2O_2$ molecules [10].

Altering the coordinated repair of DNA processes that repair damage induced by ionising radiation improves outcome. Cell repair, at low radiation level, can accommodate injuries such as double strand breaks and with increasing level the inflicted damage on the cell promote the cells to enter apoptosis and eventual cell death. This sensitivity to the dose of radiation that inflicts these injuries differs from tumor to tumor and the surrounding non-tumorous tissues [11]. Cells with high turnover are typically the first to respond to radiotherapy treatment thus fulfilling the aim of RT which is to eradicate or at least debulk the tumor so it becomes more amenable to surgical excision [12].

The addition of chemotherapy to the treatment plan has additional effects on cell's response to radiation and this combined treatment leads to either delay or abolition of the reparative process. These chemotherapeutic agents will target the cell cycle at more sensitive phase [13]. The flurouracil-based neoadjuvant CRT (nCRT) was further improved by adding oxaliplatin. This regimen significantly improved disease-free survival of patients with stages cT3-4 or cN1-2 rectal cancer in comparison to the older regimen [14].

In 2004, Habr-Gama et al. [15] have pioneered the concept of "wait and see" for rectal cancer as they have found significant number of patients who have received CRT responded very well and staged as complete pathological responders. As those patients have an excellent prognosis according to Habr-Gama et al. [15], they proposed that carefully selected rectal cancer patients responding to CRT should have a nonsurgical management. Despite the argument against wait and see [16] which stated that the rationale of a "wait and see" policy when complete clinical response status is achieved relies on retrospective observations, and data are currently insufficient to support this policy except in patients who are recognized to be unfit for or refuse radical surgery. The "wait and see" policy however is gaining ground and many centres in the world are following the Sao Paulo regime with great success as it has shown excellent outcomes in 25%–40% of carefully selected and staged patients [17].

The challenge we are facing now is how to accurately predict pathological complete response (pCR) to change the management plan before radical surgery. An increased interest in assessment of nCRT response is well documented, but this did not show much success yet. In the "watch-and-wait" approach, patients deemed to have achieved clinical complete response (cCR) must meet strict inclusion criteria. This includes digital rectal examination, direct visualization by colonoscopy, and biopsying suspicious lesions in the irradiated tumor bed [18]. Difficulty in distinguishing fibrosis from residual tumor and the distribution of residual rectal cancer within different layers of bowel wall after nCRT poses a significant difficulty in assessing complete response [19]. The use of positron emission tomography (PET) as an addition for the clinical assessment of cCR is a refinement that improved the overall accuracy from 91% to 96% [20].

## Histological Effect of RT on the Neoplastic Cells

In 1989, a prospective study of 186 rectal carcinoma patients was carried out, in which, 97 were randomized to surgery alone and 89 to surgery with preoperative radiotherapy [21]. The study showed that radiation under-staged the disease biologically but over graded it histologically in the sense that the appearances of individual cells may appear more bizarre after CRT than before treatment. It also suggested that any clinical pathology staging should include the presence or absence of radiation. To that extent the minimum dataset (MDS) which is used for all cancers in UK stipulated that the form should state whether the tumor received radiation therapy and if so whether there is response. The response is determined by looking into the volume of the neoplasm versus fibrosis. The MDS categorise the response rate as follows: no residual tumor/mucous lakes only, minimal residual tumor or no marked regression [22].

## Staging Systems

Over the years, many systems for tumor regression grading with various scoring parameters were developed. The first was developed in 1994 by Mandard et al. [23], it was designed to assess tumor response in oesophageal cancer patients treated with nCRT. They used a five-tier system to classify regression from score 1 (no tumor cells; complete regression) to score 5 (no regression). The main advantage of the Mandard's Tumor Regression Grade (TRG) system is comparing the proportion of the residual cancer cells to the amount of fibrosis. This was considered simple and was shown to be a reproducible method; 3 years later it was modified to colorectal cancer specimens by Dworak et al. [24] in 1997. They classified regression into five grades but the other way around from 0 (no re-


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gression) to 4 (total regression). In 2002, Wheeler et al. [25] devised a three-point grading system called rectal cancer regression grade, where grade 1 indicated complete response, grade 2 showed marked fibrosis despite persistent microscopic disease, and grade 3 showed no response with little or no fibrosis taking into consideration the macroscopic features of the specimen. This was later modified by Bateman et al. [26], in which both extremes were preserved; complete replacement of viable cancer cells by fibrosis and cancer cells persistence without fibrotic changes but subtle changes were added for groups of near-complete responders. Cutoffs of 0%–5%, 5%–50%, and >50% residual tumor were adopted. Although several grading systems for tumor response have been devised, a three-point TRG has been shown to provide good inter-observer reproducibility compared to the five grades, but both systems were shown to provide similar prognostic significance. The three-point system devised in Ryan et al. [27] has been shown to be reproducible and easy to use, with good inter-observer agreement. The most recently published classification by the Royal College of Pathologists dataset guidelines for colorectal cancer (2017) and the College of American Pathologists based on the AJCC/UICC, 8th edition [28] recommend a four-tier system with modification to the one described by Ryan et al. [27]. This is considered the best methodology and provided excellent inter-observer reproducibility compared with five-grade systems. It also showed similar prognostic significance. Table 1 summarizes staging systems by Wheeler et al. [25], Mandard et al. [23], and AJCC/UICC 8th edition. More recently however a group from South Korea compared Ryan et al. [27]'s, AJCC and modified Dworak staging systems and found that the modified Dworak (which included the assessment of mural tumor and the lymph node status) as a best system to reflect recurrence and disease free survival [29].

Mucin pools are a common feature during histopathological assessment of specimens treated with nCRT but the presence of acellular mucin following nCRT does not have a significant impact on patient outcome. Only the presence of malignant cells in the specimen is the considered criteria for staging of tumor following preoperative treatment. Haemorrhage, necrosis, inflammation and acellular mucin are not considered as part of staging process, they are considered only for studying regression [22].

In a study by Fokas et al. [30] in 2018, the prognostic role and surrogacy of the neoadjuvant rectal (NAR) score was examined for cT, ypT and ypN categories. NAR scores were categorised into three degrees; low when the score is below 8, intermediate (score between 8 and 16) and high in scores over 16 based on the observed scores in a clinical trial. In the previous study, NAR scores were capable of predicting treatment effects on clinical outcome and overall survival with lower NAR scores having better cumulative incidence of disease free survival, overall survival, and distant metastasis [30].

## Types of Radiotherapy

The commonest modalities for RT are short course (SC) followed by surgery after 5 days, SC with extended interval, long course (LC) combined with chemotherapy and the contact radiotherapy. Contact radiotherapy, also known as Papillon treatment, is a modality of radiotherapy given from inside the rectum in low doses reaching only few millimetres into the tissue. SC is given as 25 Gy over 5 days with a daily dose of 5 Gy. LC is given as a total dose of 45–50 Gy in 25–28 fractions [31].

**Table 1.** Grading systems

| | Grade | Description |
|---|---|---|
| Mandard's Tumor Regression Grade [23] | 1 | No residual cancer |
| | 2 | Rare residual cancer cells |
| | 3 | Fibrosis outgrowing residual cells |
| | 4 | Residual cancer outgrowing fibrosis |
| | 5 | Absence of regressive changes |
| Rectal Cancer Regression Grade (RCRG) [25] | 1 | Pathological complete response or only microscopic foci of adenocarcinoma remaining |
| | 2 | Marked fibrosis but macroscopic disease is present |
| | 3 | Poor response with little or no fibrosis and abundant macroscopic disease |
| AJCC, Royal College of Pathologists four-tier system | 0 | Complete response: No viable tumor cells |
| | 1 | Near-complete response: Single cell or rare small groups of cancer cells |
| | 2 | Partial response: Residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells |
| | 3 | Poor or no response: Extensive residual cancer with no evident tumor regression |

AJCC, American Joint Committee on Cancer.

Comparing SC to LC radiotherapy, both had similar outcomes in terms of sphincter preservation, local recurrences, late toxicity, the overall survival, disease-free survival and quality of life. However, pCR was higher in patients receiving LC of RT [32,33]. There is no uniformity of using SC or LC as practice varies widely but in many centres the use of LC is reserved when the circumferential resection margin (CRM) is threatened, otherwise SC is the preferred treatment. In other centres they only use SC or LC alone. Now preoperative RT or CRT is mostly used as it is less toxic and more efficient than postoperative RT [34]. There is very little experience on the histological changes after contact therapy or SC with extended interval.

### 1. Preoperative vs. postoperative CRT

The timing of radiotherapy with the administration of chemotherapy treatment is crucial to accomplish the maximum effect of this therapy [35]. Preoperative CRT was previously reported as the preferred method of treatment for patients with locally advanced rectal cancer. It is associated with improved compliance to CRT and down-staging which plays a role in enhancing the rate of curative surgery as well as doubling the chances of sphincter preservation compared to postoperative radiation in low-lying tumors although in one paper looking at series of stage 3 rectal cancer it was found that there was improvement of local recurrence rate but no overall survival benefit was associated with preoperative compared to postoperative RT [36]. Preoperative radiation was further associated with more effective results due to better tumor oxygenation preoperatively [37].

Preoperative RT might effectively treat systemic micrometastases reducing the rate of local failure. Some modalities of preoperative CRT further showed disappearance of mutations which could be related to the effect of CRT as well as the emergence of new resection mutations which were thought that may be due to either treatment-driven selection or expansion of pre-existing clones which were undetectable due to their low levels. Thus, evidence of intramural heterogeneity in rectal cancer was reported [38].

The other important area is whether SC RT is associated with decrease locoregional recurrence is still associated with stage improvement. In one paper [39], the group looked at both SC RT and LC CRT which have shown that there is stage improvement even in SC RT. This is in contrast to an earlier work from Nagtegaal et al. [40] when they found that no change in stage occurred with SC RT.

A better prognosis and disease-free survival have been seen in patients with completely excised rectal carcinomas who have complete or marked regression of their tumor when received CRT preoperatively [39,41]. In a recent systematic review and meta-analysis of 4,875 patients from 17 studies by Kong et al. [42], a significant association with overall survival was identified. The 15.9% of patients showed (pCR), and 29.9% showed no response.

## Predictive Biomarkers for CRT in Rectal Cancer

Some tumors resist the treatment. Furthermore clinical, histopathological and radiological profiles have been unreliable in predicting which tumors would be responsive to the treatment. With regards to radiological modalities, some studies tried utilizing MRI TRG to assess patients preoperatively in order to modify the treatment strategy. They clustered the cases into good responders in which surgery may be delayed to avoid the associated mortality and morbidity whereas poor responders are advised to undergo additional treatment to help down-staging and early treatment systemic relapse risk [43]. Despite that, there is no consensus on this modality requiring more robust studies. Therefore, it is essential to look for predictive biomarkers that are highly sensitive and specific to avoid unnecessarily giving RT treatment to unresponsive tumors. Molecular biomarkers are used in clinical practice to predict treatment response in various malignancies. Several studies have investigated molecular markers in rectal carcinoma, and their ability to predict a response to CRT.

## Molecular Markers in Rectal Carcinoma

### 1. MicroRNAs

MicroRNAs (miRNAs/miRs) are a class of short non-coding RNA sequences composed of around 22 nucleotides that are involved in the post-transcriptional regulation of gene expression. Various miRNAs have been identified to play a role in carcinogenesis by regulating the transcription of oncogenes and tumor suppressor genes. miRNAs can be studied in tissue preparations and also in peripheral blood which could provide a minimally invasive method to test for predictive biomarkers. Eriksen et al. [44] investigated the expression of miRNAs in formalin-fixed paraffin embedded (FFPE) diagnostic samples of rectal carcinoma using real-time quantitative polymerase chain reaction (RT-PCR). TRG was used to assess the response to treatment. Significant positive correlation was found between the low expression of miR-145 and response to CRT. Another group studied the relationship between miR-194 and response to CRT using RT-PCR and in situ hybridisation on FFPE diagnostic samples [45]. They found high levels of miR-194 to correlate significantly to response to treatment using both methods of testing. Luo et al. [46] demonstrated that the up-regulation of miR-519b-3p is associated with a response to CRT. In addition to tissue-based assays, circulating microRNAs have the potential to


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be used as minimally invasive predictive biomarkers. A Chinese research group identified circulating miR-345 as a possible predictive biomarker for CRT [47]. Overexpression of miR-345 was significantly correlated with poor responsiveness to CRT. Tumors with low expression of miR-345 showed higher sensitivity to radiotherapy.

### 2. Protein markers

Protein biomarkers in tissue preparations have been widely explored, and many were found to be correlated with CRT response and thus can be potentially used as predictive biomarkers. *DEK* is an oncogene that is overexpressed in many cancers including breast cancer, hepatocellular carcinoma, and melanoma. In a study using microarray of diagnostic rectal cancer specimens in the immunohistochemical analysis of DEK, high expression of DEK was found to be associated with better response to CRT. All the tumors with complete response to the treatment were overexpressing DEK [48]. Another group studied the expression of two immunohistochemical markers: cyclooxygenase-2 (COX-2) which is associated with angiogenesis and proliferation, and apoptosis protease-activating factor 1 (APAF-1). High expression of APAF-1 was associated with a better response to CRT, while high expression of COX-2 was associated with a poorer response to the therapy [49]. Therefore, tumors with increased APAF-1 levels and decreased COX-2 levels showed the best response to CRT. APAF-1 and COX-2 are both potential predictive biomarkers to CRT therapy, independently and combined.

Repetto et al. [50] performed proteomic studies on rectal cancer biopsies using two-dimensional differential in gel electrophoresis (2D-DIGE) to discover predictive biomarkers for rectal cancer treatment. They extracted proteins from RC samples and normal tissues and identified 27 differentially expressed proteins in good versus poor responders. Among these, fibrinogen β chain fragment D, cathepsin D, actin, serpin B5, serpin B9, and peroxiredoxin-4 were highly expressed in poor responders' group and are potential negative predictive biomarkers to CRT.

## Conclusion

miRNA and protein biomarker are promising as predictive biomarkers for CRT in rectal carcinoma. However, none of these biomarkers have been employed in routine clinical practice. A single biomarker is probably unlikely to have the ability to be predictive with high sensitivity and specificity. A biomarker panel, which could include genetic, epigenetic and protein biomarkers, in combination with clinicopathological and radiological data need to be evaluated together to reach a robust method of predicting therapy outcome, which in turn predicts the prognosis, and informs therapeutic approach.

## Conflict of Interest

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

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# Late side effects of radiation treatment for head and neck cancer

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Patients undergoing radiation therapy for head and neck cancer (HNC) experience significant early and long-term side effects. The likelihood and severity of complications depends on a number of factors, including the total dose of radiation delivered, over what time it was delivered and what parts of the head and neck received radiation. Late side effects include: permanent loss of saliva; osteoradionecrosis; radiation recall myositis, pharyngoesophageal stenosis; dental caries; oral cavity necrosis; fibrosis; impaired wound healing; skin changes and skin cancer; lymphedema; hypothyroidism, hyperparathyroidism, lightheadedness, dizziness and headaches; secondary cancer; and eye, ear, neurological and neck structures damage. Patients who undergo radiotherapy for nasopharyngeal carcinoma tend to suffer from chronic sinusitis. These side effects present difficult challenges to the patients and their caregivers and require life-long strategies to alleviate their deleterious effect on basic life functions and on the quality of life. This review presents these side effects and their management.

**Keywords:** Radiation, Side effects of radiation, Fibrosis, Head and neck cancer, Lymphedema, Mucositis

## Introduction

Radiation therapy (RT) is often used to treat head and neck cancer (HNC) [1]. RT can damage blood vessels that nourish muscles, nerves, and bones resulting in a progressive "radiation fibrosis syndrome", which causes a variety of complications [2]. The likelihood and severity of complications depends on a number of factors, including the total dose of radiation delivered, over what time it was delivered and what parts of the head and neck received radiation. The side effects of RT for HNC are divided into early (acute) and long-term (chronic) effects [3]. Early side effects occur during the course of therapy and during the immediate post therapy period (approximately 2–3 weeks after the completion of a course of RT). Late effects can manifest any time thereafter, from weeks to years later [4].

Patients are usually most bothered by the early effects of RT, although these will generally resolve over time. Knowledge of the radiation side effects can allow their early detection and proper management. Late side effects include permanent loss of saliva; osteoradionecrosis; pharyngoesophageal stenosis; dental caries; oral cavity necrosis; fibrosis; radiation recall myositis, impaired wound healing; skin changes and skin cancer; lymphedema; hypothyroidism, hyperparathyroidism, lightheadedness, dizziness and headaches; secondary cancer; and eye, ear, neurological and neck structures damage. This manuscript reviews the major late side effects of RT and their management (Table 1).

## Permanent Dry Mouth (Xerostomia)

Although xerostomia and thick saliva improves in most people, they can be long lasting and affects quality of life. RT can lead to irreversible salivary glands cells damage [2,5]. Serous salivary glands (parotid & submandibular) are very sensitive to radiation. RT often leads to marked changes in the quantity and quality of saliva

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**Table 1.** Late radiation toxicities of head and neck cancers

| Side effects | Symptoms | Etiology | Complications | Management |
|---|---|---|---|---|
| Permanent dry mouth (xerostomia) | Dry mouth, difficulty in eating, swallowing, and speaking | salivary glands cells damage | Opportunistic infections, denture stomatitis, alterations in pH, alteration in secretory IgA, salivary stones and cysts, radiation caries, burning mouth syndrome | Maintain adequate oral hygiene, salivary substitutes' saliva stimulation, low-level laser treatment of the salivary gland, chlorhexidine, antifungal therapy, adequate hydration, acupuncture |
| Burning mouth syndrome | Burning or scalded of mouth; dryness, increased thirst; loss of taste | Unknown | Depression, anxiety, difficulties in falling asleep and eating | Oral rinses, lidocaine, saliva substitutes, capsaicin, clonazepam or klonopin, antidepressants, pain medications, low-level laser therapy, cognitive behavioral therapy |
| Dental caries | Dental caries | Increase of caries producing bacteria, reduced salivary antimicrobial proteins and mineralizing components | Osteoradionecrosis, teeth loss, root canal infection, dental abscess | Oral hygiene, management of xerostomia, topical fluorides and/or remineralizing agents |
| Osteoradionecrosis | Pain, bad breath, dysgeusia, numbness, trismus, mastication and speech difficulties | Tooth extraction, implant placement, dental disease | Fistula, pathologic fractures, local and systemic infection | Debridement, antibiotic treatment and prophylaxis, hyperbaric oxygen |
| Fibrosis | Woody texture, limited neck enhance lymphedema | Radiation induced inflammation leading to fibrosis, poor vascularity, and scarring | Esophageal stricture, trismus, temporomandibular joint dysfunction, headaches, migraine | Physiotherapy, myofascial release, external laser |
| Trismus | Mastication muscles fibrosis | inability to open the mouth | Adverse effects on oral care, chewing, nutrition, oral care, speech production | Oral appliances, diet modification, pharyngeal strengthening, swallow retraining |
| The dropped head syndrome | Severe kyphotic deformity of the cervico-thoracic spine | Weakness of the neck extensor muscles | Restrictions to ambulation, activities of daily living and social interactions | Supportive care, external orthotic devices |
| Pharyngoesophageal stenosis | Narrowing in the pharynx or esophagus | Difficulty in eating | Weight loss | Dilation, surgery, stents |
| Skin changes and skin cancer | Acute inflammatory reaction in an area previously exposed to radiation after a chemotherapeutic agent or other medication | Skin fibrosis and color swelling, atrophy, telangiectasias | Skin cancer, scarring | Removal of skin cancer, maintaining proper skin hygiene, hydrophilic or lipophilic barrier creams with or without hydrogel or hydrocolloid dressings |
| Lymphedema | Neck and facial swelling, heaviness, achiness | Internal fibrosis | Scarring; fibrosis; breathing difficulty; congestion; reduced neck motion; ear pain, sensory limitation; speech, voice, swallowing problems emotional issues | Manual lymph drainage, compression bandages and garments, lymphatic pump |
| Hypothyroidism | Slowing of metabolic processes symptoms | Radiation induced damage to the thyroid gland | Hoarseness, weight gain, constipation, xerostomia, cold intolerance, fatigue, puffy eyes, muscle weakness and cramps, menorrhagia, depression, slower cognition, poor memory | Thyroxine |
| Hyperparathyroidism | Adenoma formation | Excessive urination, abdominal pain, tiring weakness, depression. bone and joint pain, nausea, vomiting and loss of appetite | Osteoporosis, kidney stones, hypertension | Calcimimetics, hormone replacement therapy, bisphosphonates<br>Surgical removal of the parathyroid adenoma(s) is curative in most patients |
| Cognitive impairment | Radiotherapy, comorbidity and treatment effects on cognition | Attention, thinking, or short-term memory problems | Impairment of daily functioning, quality of life, capacity to work | Medications, occupational therapy, cognitive rehabilitation |
| Neurological damage | Damage to the nervous system | Pain, memory loss, stroke-like symptoms, brain function, transverse myelitis, neuropathy, postural hypotension | Worsening of symptoms, impairment of daily functioning, quality of life, capacity to work | Pain and antiseizure medication, physical therapy, acupuncture, topical treatment, antidepressants |
| Brachial plexopathy | Radiation damage to the brachial plexus, fibrosis | Paresthesia, dysesthesia, decreased sensitivity, movement loss, muscular atrophy, shoulder joint dislocation | Worsening of symptoms, impairment of daily functioning, quality of life, capacity to work | Physical and occupational therapies |
| Eye damage | Radiation damage to the lens, retina | Cataract, retinopathy | Vision loss | Monoclonal antibody, triamcinolone, laser, photodynamic therapy, hyperbaric oxygen, pentoxifylline |

altering its consistency from watery viscous. Xerostomia can lead to opportunistic infections (mostly fungal), denture stomatitis, alterations in pH, alteration in secretory IgA, salivary stones and cysts, radiation caries (subgingival), and burning mouth syndrome [6]. It can lead to difficulty in eating, swallowing, and speaking, increase the risk of cavities and dental disease, and complicates dentures maintenance. Patients with xerostomia should maintain adequate oral hygiene to minimize the risk of oral lesions. Periodontal disease can be accelerated and caries can become rampant unless preventive measures are instituted.

Management and prevention include [7,8]: (1) palliative use of salivary substitutes (gels, rinses), (2) non-pharmacological saliva stimulation, (3) salivary stimulants, (4) low-level laser treatment of the salivary glands, (5) prophylactic chlorhexidine, (6) antifungal therapy, (7) preventing thrush, and (8) drinking plenty of liquids. These measures can help in coping with xerostomia: drinking adequate fluids; frequent sipping or mouth spraying with water; sucking on ice chips and/or sugar-free popsicles; consuming acidic or bitter substances, using sugarless gum and sugarless hard candy, and rinsing and gargling with diet ginger ale or a weak solution of salt and baking soda are helpful to refresh the mouth, loosen thick oral secretions, and alleviate mild pain [9].

The use of saliva substitutes or artificial saliva (containing hyetellose, hyprolose, or carmellose), stimulation of saliva production from intact salivary glandular tissues by taste/mastication, pharmacological; avoiding smoking and all products that contain caffeine or alcohol, using a bedside humidifier at night, and raising the head of the bed can be helpful. Low-level laser treatment of the salivary glands can intensify cell metabolism and its application on salivary glands could improve salivation. Treatment include salivary stimulants (sialagogues), such as pilocarpine, amifostine, and cevimeline [10]. Preliminary data suggest that hyperbaric oxygen (HBO) can provides benefit for patients with xerostomia who have some residual salivary gland function [9, 11]. Acupuncture has been found helpful in reducing pain and dry mouth [12]. Dietary change from dry, tough food to easier to swallow moist, softer ones can improve nutritional status and quality of life. Use of a humidification especially in the bedroom can provide relief.

## Burning Mouth Syndrome

Chronic or recurrent mouth burning caused by the radiation and enhanced by xerostomia is termed secondary "burning mouth syndrome" [13]. Symptoms may include: a burning or scalded sensation affecting the tongue, lips, gums, palate, throat or whole mouth; mouth dryness and increased thirst; and loss of taste or changes in taste (e.g., bitter or metallic). The mouth discomfort can be present throughout the day or slowly worsen. It may last for months to years. Symptoms may suddenly disappear or rarely become less frequent. Eating or drinking can bring temporarily relief. The discomfort can lead to depression, anxiety, and difficulties in falling asleep and eating. Avoiding acidic foods, spicy foods and carbonated beverages, tobacco, and excessive stress may help.

Treatment is symptomatic and include: specific oral rinses or lidocaine, saliva substitutes, capsaicin, clonazepam or klonopin, antidepressants, pain medications, low-level laser therapy, and cognitive behavioral therapy [13].

## Dental Caries

Factors enhancing the occurrence of caries after RT include the increase in the number of oral caries producing bacteria (*Streptococcus mutans* and *Lactobacillus* species), reduced concentrations of salivary antimicrobial proteins, and loss of saliva's mineralizing components [14].

Treatment strategies include optimal oral hygiene and management of xerostomia. Resistance to caries can be enhanced by using topical fluorides and/or remineralizing agents (high in calcium phosphate and fluoride) using dental trays [14]. Topical fluorides or chlorhexidine rinses may reduce *S. mutans* levels but not Lactobacilli. Because of adverse drug interactions, fluoride and chlorhexidine dosing should be separated by several hours [14].

## Osteoradionecrosis

Osteoradionecrosis can necessitate surgical intervention and reconstruction [15]. Depending on its location and extent, symptoms may include pain, bad breath, dysgeusia, numbness, trismus, mastication and speech difficulties, fistula, pathologic fractures, and local, spreading, or systemic infection. Osteoradionecrosis is a lifelong risk for those who have received high-dose radiation [16].

The mandible is the most frequently affected bone, especially in those treated for nasopharyngeal cancer. Maxillary involvement is rare because of the collateral blood circulation it receives. Tooth extraction and dental disease in irradiated areas are major contributors to osteoradionecrosis. It may be necessary to remove decayed teeth before RT if they are in the area receiving RT [16]. Ideally, at least 7 to 14 days should be allowed for healing before initiation of RT; some have suggested allowing up to 21 days. Oral disease should be treated prior to receiving radiation therapy whenever possible [15].

Mild osteoradionecrosis can be conservatively treated with debridement, antibiotics, and occasionally ultrasound. Topical antibiotics (e.g., tetracycline) or antiseptics (e.g., chlorhexidine) may contrib-


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ute to wound resolution. Exposed bone should be covered with mucosa and necrotic bone removed. When necrosis is extensive, radical resection, followed by microvascular reconstruction is often used. The combination of pentoxifylline and tocopherol was effective in treating bisphosphonate and radiation related osteonecrosis of the jaw [17]. The prophylactic use of the combination reduced the incidence of osteoradionecrosis following dental extraction [15]. HBO has been often used in patients at risk or those who develop osteoradionecrosis. However, the available data are conflicting about the clinical benefit of HBO for prevention and therapy [18].

Patients should inform their dentists about their RT prior to extraction or dental surgery including implant placement [17]. Osteonecrosis may be prevented by administration of a series of HBO therapy before and after these procedures. This is recommended if the involved tooth is in an area that has been exposed to a high dose of radiation. Dental prophylaxis can reduce the risk of osteoradionecrosis. Special fluoride treatments may help with dental problems along with brushing, flossing, and regular cleaning by a dental hygienist [18].

## Fibrosis

Fibrosis can develop in the skin, subcutaneous tissue, muscles, or other organs, depending upon the treatment site [3,4]. It generally starts eight to twelve weeks after the initiation of RT and is a lifelong issue. Radiation to the neck can cause woody texture and limited mobility of the neck, enhance lymphedema significant tightness to of the neck and shoulders muscles including the scalenes, trapezius, and sternocleidomastoid muscles. Fibrosis may cause both cosmetic and functional impairment, leading to deterioration in the quality of life. Fibrosis can also occur in the pharynx and esophagus, leading to stricture and temporomandibular joint problems including mandibular dysfunction. Patients can be assisted by mandibular stretching exercises and the use of prosthetic aids [19].

Interventions should be instituted before trismus develops. If clinically significant changes develop, several approaches can be considered, including stabilization of occlusion and use of trigger-point injection and other pain management strategies, muscle relaxants, and tricyclic medications.

To minimize the risk of neck tightness, patients should maintain flexibility of the neck muscles by stretching exercises including chin curls, head rotations, shoulder shrugs, and shoulder circles. Exercise can reduce neck tightness and increases the range of neck motion. These exercises should be performed throughout life. After fibrosis has developed individuals may benefits from myofascial release (MFR) [4]. MFR is a hands-on method of massaging and stretching the connective tissue of the head/neck to increase range of motion, increase flexibility, decrease pain, and improve posture. Treatment can also break down the fibrosis. The earlier the intervention, the better it is for the patient.

Muscle tightness can trigger headaches, leading to migraines. The mastication muscles are also often involved. Treatment of muscle fibrosis can often alleviate and reduce the frequency of such headaches [20]. Fibrosis can become more extensive after surgery or re-radiation.

## Trismus

Trismus or lockjaw is common following radiation targeting the base of tongue, tonsil, retromolar trigone, soft palate, masseter muscles, pterygoid muscles, and the temporomandibular joint (TMG) [21]. The prevalence of trismus increases with increasing radiation dose, and levels in excess of 60 Gy are more likely to cause it [21].

Mastication muscles fibrosis can lead to progressive inability to open the mouth. Trismus can adversely affect proper oral care and treatment, chewing, nutrition, oral care, speech production, and intubation. Prophylactic trismus prevention exercises can be initiated in those considered at high risk [2,4]. If aggressive intervention is needed, a speech pathologist may recommend prophylactic use of tongue blade therapy or a device (e.g., TheraBite, OraStretch, Dynasplint) [22]. A wide array of appliances is available for the treatment of trismus [23]. Swallowing dysfunction often requires a change in diet, pharyngeal strengthening, or swallow retraining, especially in those who have had surgery and/or chemotherapy.

## The Dropped Head Syndrome

The dropped head syndrome (DHS) is a disabling condition caused by severe weakness of the neck extensor muscles causing progressive reducible kyphosis of the cervical spine and the inability to hold the head up [24]. DHS can occur from 3 months to 30 years after RT.

Treatment with physiotherapy and surgery have not been very successful, and the management of DHS is supportive, including employing a cervical collar to maintain the head in an upright position [4,24]. The condition generally does not spread to other muscles or worsens.

## Pharyngoesophageal Stenosis

Pharyngoesophageal stenosis can be a delayed complication of RT [25]. Pharyngoesophageal (PE) stenosis is an area of narrowing in the pharynx or esophagus. This stenosis can make eating difficult,

particularly solid food. If the PE segment closed off, the patient is not able to eat or drink by mouth and needs gastric tube. Treatment includes frequent placement of dilating catheters to stretch open the narrowed segment or by surgically removing the blocked segment followed by flap reconstruction [25].

## Skin Changes and Skin Cancer

Patients can experience "radiation recall dermatitis" [26]. Patients who had early severe dermatitis, may experience inflammatory waves occurring weeks to years later [27]. This is characterized by a skin rash typified by redness, swelling, and/or skin blistering. The rash is often painful resembling severe sunburn.

Late-stage or "chronic radiation dermatitis" typically presents months to years after RT. It is characterized by skin fibrosis, slight color changes to the skin or mild swelling, atrophy, and telangiectasias. Individuals generally lose hair in the region that received radiation. Radiation can increase the risk for skin cancers (basal cell and squamous cell carcinoma) [4]. Regular follow-up by a dermatologist is important.

## Lymphedema

Lymphedema can cause chronic inflammation and reactive fibrosis of the affected tissues. RT creates scarring which interferes with the function of the lymphatics resulting in slow lymphatic swelling. Lymphedema generally starts and progresses slowly 8 to 12 weeks after initiation of RT and can be a life-long issue [4,5].

Lymphedema can be external (skin and soft tissue) and internal (pharyngeal and laryngeal mucosa). Lymphedema causes heaviness and achiness sensations, and may lead to skin changes.

Lymphedema has several stages [28]:

- Stage 0: No swelling, but a sense of heaviness in the neck.
- Stage 1a: Visible mild swelling without pitting. Reversible.
- Stage 1b: Visible mild swelling with pitting. Reversible.
- Stage 2: Firm-pitting swelling that is irreversible. No visible tissue changes.
- Stage 3: Irreversible tissue changes with scarring and fibrosis.

Lymphedema can cause difficulty in breathing, congestion, impairment in vision, motor (reduced neck motion, jaw tightness or trismus, and chest tightness), ear pain, and sensory limitations, speech, voice, and swallowing problems (i.e., inability to use an electrolarynx, difficulty in articulation, drooling, and loss of food from mouth), and emotional issues (depression, frustration, and embarrassment) [28].

Over time, the lymphatics find newer way of drainage, and the swelling and neck tightness generally goes down. Sleeping with the upper body in an elevated position can use gravity to speed the process of lymph fluid drainage. Specialists in reducing edema can assist the patient to enhance the drainage and shortening the time for the swelling to decrease. This treatment can also prevent permanent swelling and fibrosis.

Treatment of lymphedema includes [28]: (1) manual lymph drainage (face and neck, deep lymphatics, trunk, intra oral), (2) compression bandages and garments, (3) use of tactile lymphatic pump, (4) remedial exercises, (5) skin care, (6) elastic therapeutic tape (Kinesio Tape), and (7) oncology rehabilitation [2,4]. Diuretics, surgical removal (debulking), liposuction, compression pumps, and elevation of the head alone are ineffective treatments [28].

## Hypothyroidism

Most individuals receiving RT develop hypothyroidism. The symptoms of hypothyroidism vary; some individuals have no symptoms while others have dramatic or, rarely, life-threatening symptoms [29]. Most symptoms of hypothyroidism are due to the slowing of metabolic processes.

Thyroid deficiency can be corrected by taking synthetic thyroid hormone (thyroxine) [4,29]. The patient should be reevaluated and serum thyroid stimulating hormone (TSH) should be measured in 3 to 6 weeks, and the dose adjusted if needed. The process of adjusting the dose of hormone every 3 to 6 weeks is continued, based upon periodic measurements of TSH until it returns to normal. After identification of the proper maintenance dose, TSH levels should be measured at least yearly.

## Hyperparathyroidism

The parathyroid glands are resistant to RT. However, hyperparathyroidism (HPT) due to adenoma formation can occurs in individuals who had received RT for HNC after a longer latency period [30]. Signs and symptoms of HPT include: osteoporosis, kidney stones, excessive urination, abdominal pain, tiring easily or weakness, depression and forgetfulness, bone and joint pain, frequent complaints of illness with no apparent cause, nausea, vomiting and loss of appetite [30]. HPT is diagnosed by finding elevated calcium levels in the blood, bone mineral density test (bone densitometry), a 24-hour collection of urine, and imaging tests of kidneys.

Treatment includes watchful waiting in those with normal calcium levels and kidney functions, and normal bone density. Medications to treat HPT include calcimimetics, hormone replacement therapy to retain calcium, and bisphosphonates. Surgical removal of the parathyroid adenoma(s) is curative in most patients [30].


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## Attention, Thinking, and Memory Problems (Cognitive Problems)

Many patients who received RT to the head and neck and/or chemotherapy experience attention, thinking, or short-term memory problems [31]. Other causes for cognitive problems are pain, side effects of medications, emotional state, and other medical problems. Cognitive problems can manifest in the following symptoms or behavioral changes: (1) trouble concentrating, focusing, or paying attention, (2) mental fog or disorientation, (3) difficulty with spatial orientation, (4) memory loss or difficulty remembering things, especially names, dates, or phone numbers, (5) problems with understanding, (6) difficulties with judgment and reasoning, and (7) impaired ability to calculate and organize, and impaired language skills. These include difficulties to organize one's thoughts, find the right word, or balance a checkbook: (1) problems in multitasking, (2) processing information slower, (3) behavioral and emotional changes, such as irrational behavior, mood swings, inappropriate anger or crying, and socially inappropriate behavior, and (4) severe confusion.

Management of these cognitive problems includes: (1) medications, including stimulants, cognition-enhancers, antidepressants, narcotics blockers, (2) occupational therapy and vocational rehabilitation, and (3) cognitive rehabilitation and cognitive training.

## Neurological Damage

These can include serious problems such as memory loss, stroke-like symptoms, and brain function [31]. RT to the neck can affect the spinal cord, resulting in a self-limited transverse myelitis, known as "Lhermitte's sign". The patient notes an electric shock-like sensation mostly felt with neck bending (flexion) [32]. This condition rarely progresses to a true transverse myelitis which is associated with Brown-Séquard syndrome. RT may cause neuropathy due to nerve injury, although it may take several years for symptoms to appear [2,4]. It can also cause peripheral nervous system dysfunction resulting from external compressive fibrosis of soft tissues and reduced blood supply caused by fibrosis. Symptoms depend on which nerves are affected and include: change in sensation, especially in the hands and feet (e.g., numbness, tingling, or pain), muscle weakness (i.e., myopathy), paralysis and/or paresis (weakness) of the diaphragms (phrenic nerve damage), and changes in organ function (i.e., constipation, dizziness) [33].

Acupuncture treatment may improve peripheral neuropathy [34].

Damage to the peripheral and autonomic nervous system can lead to dizziness when standing up from sitting up from sitting or lying down due to postural hypotension.

## Brachial Plexopathy

Radiation-induced brachial plexopathy is caused by radiation damage to the brachial plexus [2,4,35] that provide sensation and muscular innervation for the whole hand. Symptoms include paresthesia, dysesthesia, decreased sensitivity, partial loss of movement, complete paralysis of the arm, muscular atrophy, impaired mobility and partial dislocation of the shoulder joint. The damage to the brachial plexus results from a combination of direct RT nerve damage, the development of fibrosis and damage to blood vessels supplying these nerves. The extent of damage is associated with the radiation dose and technique, and concurrent chemotherapy.

Most develop symptoms within the 3 years (range, 6 months to 20 years) [35]. Rehabilitation includes physical and occupational therapies [33].

## Eye Damage

Radiation can cause sub-capsular and cortical cataract [4]. The risk of lens opacities exists above does of 0.5 Gy. "Radiation retinopathy" is dose related (especially >45 Gy) and is common after RT for nasopharyngeal, paranasal sinus or orbital tumors. Shielding of ocular structures during RT and hyperfractionation can decreased its incidence [36].

Treatment includes intravitreal injection of humanized monoclonal antibody to vascular endothelial growth factor (bevacizumab), intravitreal triamcinolone acetonide, grid macular laser photocoagulation, sector scatter and panretinal laser photocoagulation, photodynamic therapy, HBO and oral pentoxifylline [36]. Advanced proliferative radiation retinopathy complicated by vitreous hemorrhage and/or tractional retinal detachment may require vitrectomy.

## Damage to the Ear (Ototoxicity) and Hearing Loss

Patients who undergo RT for HNC can develop hearing especially when receiving 60 Gy. Complaints include ear heaviness, earache, decreased hearing, tinnitus, and dizziness. Dose of radiation is directly proportional to ototoxicity [37].

Radiation to the ears may result in serous otitis (otitis with effusion) [38]. It is associated with fluid collection in the middle ear and temporary reduced hearing. Serous otitis and conductive deafness are reversible over time. High doses of radiation can cause sensorineural hearing loss due to damage to the inner ear, the auditory nerve, or the vestibular apparatus. This condition is not reversible. Damage to the vestibular apparatus can cause dizziness and vertigo.

## Lightheadedness, Dizziness, and Headaches

Damage to the peripheral and autonomic nervous system and the carotid artery baroreceptors can lead to dizziness due to orthostatic hypotension [39]. This can be prevented by standing up slowly, wearing of compression stockings, exercising, and keeping well hydrated. The perception of the body's position is determined by the brain by integrating information from the middle ear, eyes, and the body's muscles and joints. The perception of lightheadedness and dizziness after RT may be generated in some individuals by misinformation sent to the cerebellum from the fibrotic neck muscles and damaged middle ear [39].

Dizziness and lightheadedness can be treated by vestibular rehabilitation and exercises that stretch the fibrotic muscles, reduce neck stiffness, and increase the head and neck range of motion [40]. Muscle tightness and fibrosis can trigger headaches leading to migraine. The muscles of mastication are also often involved. Treatment of muscle fibrosis can alleviate and reduce the frequency of headaches [4].

## Damage to Neck Structures

RT can cause lymphedema and fibrosis, carotid artery (CA) stenosis and stroke, CA rupture, oropharyngo-cutaneous fistula, and CA baroreceptors damage leading to permanent and paroxysmal (sudden and recurrent) hypertension [41]. Factors contributing to increased risk of ischemic stroke including CA stenosis and increased deposition of plaque, as well as other pre-existing risk factors for cerebrovascular disease.

**Stenosis, and rarely CA rupture** [42]. Yearly screening neck ultrasound can lead to early diagnosis. The incidence of CA stenosis is 18%–38% in irradiated patients compared to 0%–9.2% in unirradiated patients [43]. CA disease can cause strokes and transient ischemic attack (TIA). It is important to diagnose carotid stenosis or impending rupture early, before a stroke or severe bleeding has occurred. Stenosis can be diagnosed by hearing a bruit sound over the CA, ultrasound, CT, magnetic resonance angiogram (MRA), MRI, and angiography. Treatment of stenosis caused by RT is usually by placing a stent. Other methods include removal of the blockage (endarterectomy), and prosthetic carotid bypass grafting [44]. RT can damage the CA baroreceptors. These baroreceptors regulate the blood pressure sending messages to the central nervous system to alter the peripheral vascular resistance and cardiac output. Some individual treated with radiation "develop low, labile or paroxysmal hypertension" [45].

**Low blood pressure** can be cause by damage to the peripheral and autonomic nervous system and the carotid baroreceptors. This can lead to baroreceptor failure manifested by orthostatic hypotension characterized by dizziness when standing up from a sitting or lying down. It can be managed by standing up slowly, wearing of compression stockings, exercising and by keeping well hydrated [41,45,46].

**Labile hypertension** is characterized by sometime asymptomatic blood pressure fluctuations from low (e.g., 120/80 mmHg) to high (e.g., 170/105 mmHg). A relationship between blood pressure elevation and stress or emotional distress is usually present [47].

**Paroxysmal hypertension** is characterized by sudden elevation of blood pressure (>200/110 mmHg) associated with an abrupt onset of distressful physical symptoms, such as headache, chest pain, dizziness, nausea, palpitations, flushing, and sweating. Episodes can last from 10 minutes to several hours and may occur in different frequency—varying from once or twice daily to once every few months. Between episodes, the blood pressure is normal or may be mildly elevated. Patients generally cannot identify obvious psychological factors that cause the paroxysms [48]. Direct massage of the carotid artery during Doppler ultrasound can lead to such episodes [49]. Medical conditions that can also cause such blood pressure swings need to be excluded (e.g., pheochromocytoma). Both of these conditions are serious and should be treated. Management can be difficult and should be done by experienced specialists.

## Secondary Cancers

RT can rarely result in new local and systemic cancers appearing. The risk is proportional to the administered radiation dose [50]. The secondary cancer can be different from the original and could include local cancers such as skin, mediastinal, oral and thyroid cancer, and systemic cancers such as lymphomas, sarcomas and leukemia [4]. It is important to be closely followed to detect secondary malignancies.

## Conclusions

RT for the HNC causes significant long-term side effects in most patients [5]. Many of these side effects present difficult challenges to the patients and their caregivers. Recognizing and treatment of these side effects can significantly improve the patients' health, long-term survival and quality of life.

## Conflict of Interest

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


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# Running of high patient volume radiation oncology department during COVID-19 crisis in India: our institutional strategy

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**Purpose:** Due to COVID 19 pandemic, the treatment of cancer patients has become a dilemma for every oncologist. Cancer patients are at an increased risk of immunosuppression and have a higher risk to acquire any infection. There are individual experiences from some centers regarding the management of cancer patients during such a crisis. So we have developed our institutional strategy to balance between COVID and cancer management.
**Materials and Methods:** Radiation Oncology departmental meeting was held to prepare a consensus document on Radiotherapy schedules and department functioning during this pandemic.
**Results:** Strategies were taken in form of following areas were steps need to be taken to decrease risk of infection, categorise treatment on the basis of priority, radiotherapy schedules modification, academic meetings and management of COVID positive patient/personnel in Radiation Oncology department.
**Conclusion:** We hope to strike the balance in overcoming both the battles and emerge as winners. Stringent long term follow up will be done for assessing the response or any unforeseen treatment related sequelae.

**Keywords:** COVID-19, Malignancy, Radiotherapy, Immunity

## Introduction

Coronaviruses are enveloped, single-stranded, positive-strand RNA viruses and are classified under *Nidovirales*. The 2019-novel coronavirus (2019-nCoV) is classified as a novel betacoronavirus belonging to the sarbecovirus subgenus of *Coronaviridae* family [1-3]. The 2019-nCoV is the third coronavirus to exhibit cross species infection from animals to humans. The previous two being 2002 outbreak caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the 2012 outbreak caused by the Middle East respiratory syndrome coronavirus (MERS-CoV) [4,5]. Coronaviruses are known to cause common colds in human adults and children. It typically causes common cold like symptoms in immunocompetent individuals. Coronavirus disease 2019 (COVID-19) has a unique pathogenicity with its ability to cause both upper as well as lower respiratory tract infection

We intend to clarify the common doubts being faced by the high volume centres regarding the functioning of the department, the treatment of patients and safety of radiation personnel.

### 1. How virulent is the COVID-19?

According to the World Health Organization (WHO) seasonal flu has R0 at 1.3 whereas average contagion metric 2–2.5 which means that a person harbouring COVID-19 can transmit it to two people. However, this is less than SARS with R0 of 4 and MERS R0 of 2.5 to 7.2 [6]. In current scenario most important public measure remains the self-initiated quarantine of minimum 14 days for all the suspected patients with mild symptoms. All suspected patients and symptomatic contacts of all confirmed cases should be subjected to tests for confirmation [7].

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### 2. COVID-19 and its relevance to malignancy patients: why worry?

SARS-CoV-2 a novel coronavirus first detected in Wuhan, China in December 2019 is the pathogen responsible for this current pandemic [7-9]. As per the official WHO website at the time of writing this article as on April 4, 2020 there are 1,098,006 cases and 59,141 deaths reported worldwide. Currently a whopping 205 countries and regions are in the grip of this pandemic along with two international conveyance. The United States and Europe have emerged as a new epicentre for COVID-19 with mortality and morbidity increasing daily. The United States and Italy are hit worst in current times with reported cases of 277,161 and death toll of 7,392 in the United States and 119,827 cases with 14,681 deaths reported in Italy. India currently has 2567 cases and 72 deaths [10]. Main measure to curb this pandemic is quarantine and social distancing. Everyone should stay at home to prevent community transmission. Thus, patients face difficulty in commuting to hospital. Radiotherapy being prolonged daily treatment needs attention during such crisis. Indian subcontinent has a population of over 1.35 billion and 1,157,294 new cases of malignancy are being diagnosed in a year as per GLOBOCAN 2018 [11], thus making treatment of malignancy as crucial as maintaining a strict vigil for COVID-19 patients.

### 3. Why worry in cancer patients and care givers?

Majority patients diagnosed of malignancy present in advanced stage disease are malnourished and have a weak innate immunity due to the disease process, poor nutritional status as well as the side effects of therapy (specially chemotherapy). Increased propensity of cancer patients of developing complications related to COVID-19 has also been seen by the Chinese data given by Liang et al. [12] reported a significantly higher incidence of severe events, i.e., death or ICU admission requiring invasive ventilation among individuals with a cancer history than those without (39% vs. 8%; $p = 0.0003$), in 2007 Chinese patients hospitalized with COVID-19. Although the sample size was small but it does serves as an indicator of the need of being cautious. On the other end of the spectrum are the healthcare providers who are constantly at an increased risk of exposure for acquiring the infection.

## Materials and Methods

On Saturday, March 21, 2020 in the wake of crisis, radiation oncology departmental meeting was held to prepare an expert consensus that will serve as a strategy in this time of crisis. The conversation was based on how to reduce transmission, manage decreased workforce and continue treatment in the presence of infection. So strategy was defined to cover all the aspects of functioning radiation oncology department, treating patients and maintaining personal protection.

## Results

Strategies are summarized in form of following areas were steps need to be taken: (1) decrease risk of infection, (2) categorise treatment on the basis of priority, (3) radiotherapy schedules modification, (4) academic meetings, and (5) management of COVID-19 positive patient/personnel in radiation oncology department.

### 1. Decrease risk of infection

The entire workforce of the department was called to the meeting and educated about the current situation with the risk involved and the need of continuing our essential services in this time. The healthcare providers are divided into two risk groups as per patient interaction (Fig. 1)

*1) General measures for decreasing risk of workforce*

Clean waiting area with adequate distancing between the waiting benches and the patients. Time slots defined for patients and treating no more than 5 patients per hour. Stringent use mask and follow standard hand hygiene practices using alcohol-based hand sanitizers and soap and water. Organised quick practical session for the departmental staff on correct use of personal protective gear, their disposal and standard practice of hand hygiene conducted. Patients on treatment should be scheduled in time slots to decrease patient waiting and contact. Detailed travel history to COVID-19 infected area or close contact with a person infected with coronavirus. Thermal screening of all patients/staff at radiation premises to be carried out regularly. In case any suspected patients, he/she will to be sent to screening outpatient department (OPD) and handled by department of medicine/emergency as per institutional policy. Staff divided into two groups and postings to be done in weekly shifts separated by time and location. The departmental staff has been strategically divided into two halves having one team at work and one in back up. Thus, ensuring smooth functioning of the department as well as having workforce in backup in case some personnel is exposed/suspected. CT-simulation have been dispersed throughout the day to minimize the number of people in the waiting rooms.

*2) Minimize personal contact*

Time: minimalize patient contact time;

Distance: minimum 1 m;

Shielding: adequate personal protective equipment (mask/scrubs).


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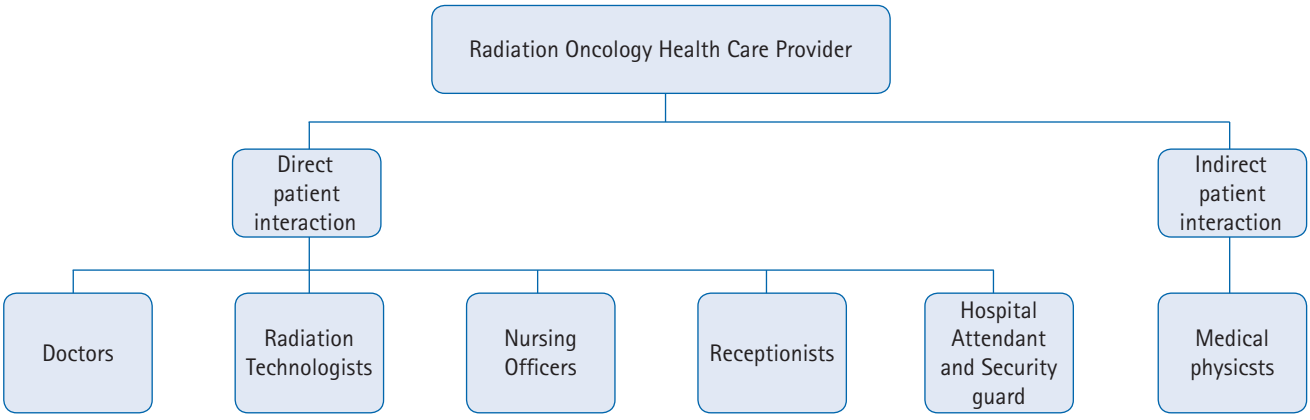


**Fig. 1.** Healthcare providers division into two risk groups as per patient interaction.

Telemedicine consultation have been started to minimize patients visits. But strictly no prescription of intravenous medication to be prescribed telephonically. Patients to be counselled mainly for symptomatic care /continuation of any metronomic therapy patient was already receiving. Postponement of elective post treatment follow up to be done.

*3) Directive to patients*

All the patients visiting radiation oncology wing are to be advised to follow social distancing at least 1 m/3 feet distance between each other. Stick to the time schedule allotted to each patient. They have report any new onset fever cold cough or breathing difficulty. Only one attendant should accompany if necessary and avoid bringing young children or old people as attendant to the hospital. They are also advised to maintain good diet to boost immunity. Patients are suggested to visit hospital only for urgent medical care. Visit to crowded areas to be avoided. They are educated to wash hands frequently with a soap/sanitizer. Elderly patients especially with symptoms are at highest risk and extra precaution should be taken.

*4) Outpatient department consultation*

Consultants and residents are instructed to maintain at least one-meter distance with care giver and patient. Take detailed history of recent travel to COVID-19 infected area or close contact with a person infected with coronavirus, check for any symptoms of viral infection in all patients. New patients enrolment to be done with quick short case history and examination to decrease contact time. Unnecessary repeated multiple examination of patients should be avoided.

*5) Inpatient department admissions*

In view of high risk of malignancy patients acquiring COVID-19, minimal inpatient department (IPD) admissions to be done. Also, majority beds will be kept vacant as a backup in case of any crisis of COVID-19 outbreak occurs in the region. Full precautions would be maintained for assuring the safety of hospital personnel as well as patient to decrease possibility of cross infection. Neutropenic patients would be admitted in the IPD and discharged only after full recovery. Review with infectious diseases team would be taken if any symptom suggestive of COVID-19.

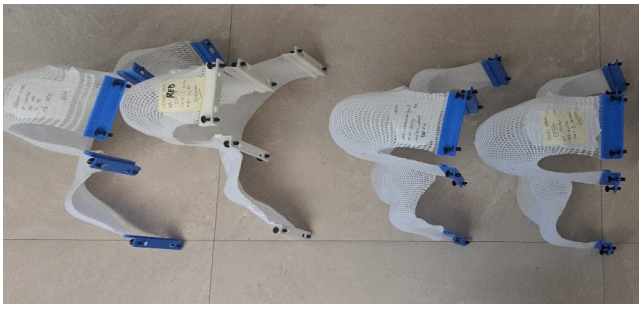

**Fig. 2.** The correct placement of immobilisation devices.

*6) Radiation oncology staff education*

Use of proper personal protection equipment (PPE) by the department staff. Regular training and stringent practice of hand hygiene. Sanitisation of (1) immobilisation casts/devices: once a day with chlorite-based solution. Also, casts to be kept separately and not stacked over one another (Fig. 2); (2) treatment/simulation couch: before starting treatment for the day and after treatment of each patient hourly; (3) door handles and knobs every 3 hourly; and (4) sheets/linen used for patients to be washed and sterilised.

## 2. Categorise treatment on the basis of priority

(1) Priority high: Patients undergoing radiation with radical intent for cure in which delay in treatment onset may jeopardize outcome.

(2) Priority moderate: Radical radiotherapy for less aggressive tu-

mours or urgent palliative radiotherapy like in patients with malignant spinal cord compression to avoid neurological damage.

(3) Priority low: Radiation in an adjuvant setting where a complete resection of disease with good margins and less than 15%–20% risk of recurrence over 10 years, and patients with less aggressive tumours where radiation is a part of treatment protocol but can be postponed owing to low risk category and slow growth of tumour.

## 3. Radiotherapy schedules modification

Evidence-based of possible hypofractionated regimens or observational strategies for a variety of entities which can be considered during this crisis. The potential benefits and risks of altered fractionations to be carefully discussed with the patient.

Hypofractionation rationale and importance in today's scenario are (1) biologically equivalent hypofractionated treatment regimens to be used; (2) helps minimize number of individual patient visits to department; (3) also helps decrease the total number of patients being treated in a day though still allowing us to keep the total patients treated the same; and (4) avoids delay of treatment in an already high-volume centre with a long waiting period.

Dose to critical organs-at-risk (OARs) would be respected and calculated as per LQ model. Minimal use of radiation accessories involving physical contact. If any accessory if contaminated should be sent for testing and decontamination. Postoperative cases or cases where the addition of radiation/chemotherapy would not translate into much clinical benefit (elective low-grade including glioma, low risk tumours like breast and prostate) will be deferred for treatment. Any patient who tests positive for COVID-19 will not be treated till patient is asymptomatic and negative titres are achieved.

*1) Site wise proposed radiotherapy schedule modifications in the time of COVID-19 crisis*

Head and neck malignancies - need and rationale for changing the protocol: Our centre has a high burden of advanced stage III/IV head and neck malignancies requiring radical radiation for treatment. Any new patient being planned will be taken up for hypofractionated radiation. Alternate day treatment at higher dose per fraction will be considered without compromising oncological outcome. This will decrease hospital visits of patients at daily basis however completing the treatment in the same duration.

*2) Eligible patients*

Young patients, the Karnofsky performance scale (KPS) >80, good expected clinical outcome is being considered for this regimen, dose of OARs specifically spinal cord ALARA (as low as reasonably achievable) not exceeding 40 Gy, and no concurrent chemotherapy will be given to these patients. Proposed hypofractionated radiotherapy dose and schedule is shown in (Table 1 and 2).

**Table 1.** Hypofractionated radiotherapy schedule for head and neck cancer with EQD2 and BED

| | High risk | Intermediate risk | Low risk |
|---|---|---|---|
| Dose (Gy/fraction) | 3 | 2.65 | 2.34 |
| Total (Gy) | 63 | 55.65 | 49.14 |
| EQD2 | 68.25 | 58.6 | 50.5 |
| BED | 82 | 70.4 | 60.6 |

EQD2, equivalent dose in 2 Gy per fraction; BED, biological effective dose.

*3) General instructions for chemotherapy and treating other sites*

Hormone positive (ER/PR+) breast tumours to be considered for hormonal therapy. Triple negative breast cancer (TNBC) may be considered for capecitabine oral tablets delaying definitive chemo by 2–4 weeks. Carcinoma prostate to be considered for androgen deprivation therapy (ADT) and radiotherapy to be delayed. Palliative chemotherapy either delay or change to least toxic oral metronomic chemotherapy (capecitabine/gefitinib/methotrexate/cyclophosphamide/etoposide). Carcinoma cervix patients to be continued on concurrent weekly chemotherapy. Patients with primary CNS (high grade) tumours having ECOG >2 to be considered for oral temozolomide therapy only. Oral bisphosphonates to be considered for bone metastasis. Neutropenic patients to be admitted and treated as per protocol (in such patients review with COVID-19 team to be taken). Less common malignancies of all other sites to be treated with a tailored case-based approach. Strategies defined here for common malignancies being encountered at our centre and should be used as per institute and regional necessity.

*4) Brachytherapy*

Carcinoma cervix patients to be taken up for brachytherapy as per schedule. However, all patients as a part of institutional policy will be subjected to COVID-19 testing and only after being reported negative will be taken up for the procedure, thus minimising the risk of any unforeseen exposure to the health personnel and also reducing the stress from the infrastructure. In procedure room, staff will be minimized to one oncologist, one anaesthetist, one nurse and one operation theatre (OT) attendant.

## 4. Academic meetings

Regular post-graduate teaching activities have been withholding and teaching is being done using online platforms. Also, multidisciplinary meet is being conducted by telephonic consultation and if required with minimum number of consultants maintaining social distance.


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**Table 2.** Radiotherapy schedules for sites of malignancy

| Series# | Site | Total dose | Dose (Gy/per fraction) | Duration (wk) |
|---|---|---|---|---|
| 1 | Cervix | | | |
| | External radiotherapy | 45 Gy in 20 fx | 2.25 | 4 |
| | Brachytherapy | Two sessions of 9 Gy each delivered 1 week apart | | |
| 2 | Brain primaries (high grade) | 40 Gy in 15 fx | 2.67 | 3 |
| 3 | Rectum | | | |
| | Preoperative, short-course (preferred) | 25 Gy in 5 fx | 5 | 1 |
| | Postoperative | 45 Gy in 20 fx | 2.25 | 4 |
| 4 | Head and neck | | | |
| | Postoperative | 55 Gy in 25 fx | 2.25 | 5 |
| 5 | Breast | | | |
| | Whole breast only | 26 Gy | 5.2 | One # per week × 5 wk |
| | Chest wall only[a] | 26 Gy | 5.2 | One # per week × 5 wk |
| | Nodal irradiation needed | 40 Gy in 15 fx | 2.67 | 3 |
| 6 | Palliative radiation | | | |
| | Painful bone metastasis; Metastatic spinal cord compression < 48 hr; Symptomatic brain metastasis; Tumour bleed | 8 Gy | 8 | SFRT |
| | SVCO (symptomatic patients only) | 20 Gy in 5 fx | 4 | 1 |

SFRT, single fraction radiotherapy; SVCO, superior vena cava obstruction.
[a]Caution: nodal irradiation should not be taken with high weekly dose.

### 5. Management of COVID-19 positive patient/personnel in radiation oncology department

Any patient having a high clinical suspicion of being COVID-19 positive and a travel history form a hotspot region of COVID-19 cases would be taken for radiation or chemo only after being tested negative. In case a patient already on treatment tests positive, all the radiation personnel who had been in direct contact would be put under home quarantine and then subject to testing for COVID-19. The facility would be sealed and sanitisation would be done for the treatment unit the restroom and a thorough testing would be taken specially for the patients who were being treated. The backup team will be brought to the front for working with stringent use of PPE and sanitisation practices will be done.

## Discussion and Conclusion

At this time of crisis world over radiation oncology departments need to take adequate precautions to reduce the likelihood of COVID-19 transmission. In oncology patients, it is a tricky situation and risk benefit calculation is very dicey because of risk of acquiring infection and at the same time possibility of spread of cancer. So we need to balance the situation in this scenario. Basic and universal precautions to be taken by staff before, during, and after each patient. Social distancing should be practised strictly. Staffing should be managed and work from home should be done in case it is possible so that in case any healthcare worker (HCW) acquires infection or is quarantined another HCW can take care of work and department as whole is not shut down. All patients should wear protective masks during their stay in the radiotherapy department.

In the current times, an unforeseen pandemic rapidly gripping the world in its claws it is the responsibility of entire medical fraternity to tackle the new age pathogen without compromising the treatment and outcome of patients dealing with other ailments specially malignancy. This must be done keeping full vigil for the safety of the medical paramedical and allied staff working in the department. These strategies are intended to serve as guide for the common questions being faced by various oncology institutes. Stringent long-term follow-up will be done for assessing the response or any unforeseen treatment related sequelae. It is a testing time for all of humanity and together we intend to come over all the adversities to the best of our knowledge and experience. We hope to strike the balance in overcoming both the battles and emerge as winners.

## Conflict of Interest

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

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# Gene signature for prediction of radiosensitivity in human papillomavirus-negative head and neck squamous cell carcinoma

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**Purpose:** The probability of recurrence of cancer after adjuvant or definitive radiotherapy in patients with human papillomavirus-negative (HPV(–)) head and neck squamous cell carcinoma (HNSCC) varies for each patient. This study aimed to identify and validate radiation sensitivity signature (RSS) of patients with HPV(–) HNSCC to predict the recurrence of cancer after radiotherapy.
**Materials and Methods:** Clonogenic survival assays were performed to assess radiosensitivity in 14 HNSCC cell lines. We identified genes closely correlated with radiosensitivity and validated them in The Cancer Genome Atlas (TCGA) cohort. The validated RSS were analyzed by ingenuity pathway analysis (IPA) to identify canonical pathways, upstream regulators, diseases and functions, and gene networks related to radiosensitive genes in HPV(–) HNSCC.
**Results:** The survival fraction of 14 HNSCC cell lines after exposure to 2 Gy of radiation ranged from 48% to 72%. Six genes were positively correlated and 35 genes were negatively correlated with radioresistance, respectively. RSS was validated in the HPV(–) TCGA HNSCC cohort (n = 203), and recurrence-free survival (RFS) rate was found to be significantly lower in the radioresistant group than in the radiosensitive group (p = 0.035). Cell death and survival, cell-to-cell signaling, and cellular movement were significantly enriched in RSS, and RSSs were highly correlated with each other.
**Conclusion:** We derived a HPV(–) HNSCC-specific RSS and validated it in an independent cohort. The outcome of adjuvant or definitive radiotherapy in HPV(–) patients with HNSCC can be predicted by analyzing their RSS, which might help in establishing a personalized therapeutic plan.

**Keywords:** Head and neck cancer, Radiation, Prediction, Treatment

## Introduction

Head and neck squamous cell carcinoma (HNSCC) arises in the mucosal lining of oral cavity, oropharynx, larynx, or hypopharynx, and is the sixth most common cancer worldwide [1]. HNSCC represents about 6% of all cancer cases and accounts for an estimated 650,000 new cases and 350,000 deaths worldwide every year [2]. About one-third of patients are diagnosed with early-stage of HNSCC, whereas a typical patient is diagnosed with advanced stage of HNSCC with lymph node metastases [3].

Early-stage HNSCC is treated by surgery or radiation, and advanced-stage HNSCC commonly requires combined therapy such as surgery, radiotherapy, and chemotherapy. Despite of the improved quality of life in patients with HNSCC after advancement in

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treatment modality such as advanced surgical technique [4] and radiotherapy [5], survival rates have not markedly improved in recent decades [6]. In particular, the intensity-modulated radiotherapy (IMRT; a three-dimensional modern radiotherapy technique) allowed sculpting of the radiation dose to the target volume and resulted in significantly reduced late toxicities compared to that in older radiation techniques, but showed no difference in locoregional recurrence and disease-free and overall survival in most cases when compared to those in the older radiation techniques [7].

Recently, besides alcohol consumption and tobacco history, which are well-known risk factors for the development of HNSCC, infection with the human papillomavirus (HPV) has been identified as an independent parameter in the development of HNSCC [8]. Patients with HPV-positive (HPV(+)) HNSCC might have a different etiology and favorable prognosis compared to patients with HPV-negative (HPV(–)) HNSCC [9]. In a multicenter study, patients with HPV(+) HNSCC showed better prognosis in locoregional recurrence and overall survival than patients with HPV(–) HNSCC [10]. In addition, patients with HPV(+) HNSCC were more sensitive to radiation than HPV(–) HNSCC [11]. However, besides HPV status, other risk factors need to be investigated to improve recurrence and survival rates after radiotherapy for patients with HPV(–) HNSCC.

Locoregional recurrence in patients with HPV(–) HNSCC after adjuvant or definitive radiotherapy might be predicted by gene signature as well as clinical or pathological results. So far, the correlation of genetic profiles from some gene sets that perform a role in cancer metabolism with therapeutic response in patients with HNSCC has been investigated [8,12,13]. Also, several studies about association between epithelial-to-mesenchymal transition (EMT) related genes and radioresistance in HNSCC have been reported [14,15]. However, there may be many other molecular biomarker signatures associated with radiosensitivity in patients with HPV(–) HNSCC.

Thus, we aimed to identify and validate radiation sensitivity signature (RSS) of HPV(–) HNSCC from as much gene expression data as possible in order to predict benefits of adjuvant or definitive radiotherapy, which could allow for development of personalized radiotherapy. We hypothesized that investigation of gene expression data and survival assay after irradiation of various HNSCC cell lines would help generate an HNSCC specific RSS, which could be validated in HNSCC big data in The Cancer Genome Atlas (TCGA).

## Materials and Methods

### 1. Cell line cultures

HNSCC cell lines CAL27, SCC25, and SCC9 were purchased from the American Type Culture Collection (ATCC); HSC2, HSC3, and HSC4 were obtained from the Japanese Cancer Resources Bank (JCRB); and FaDu, SNU1076, SNU1214, SNU46, YD10B, YD38, and YD8 were purchased from the Korean Cell Line Bank (KCLB). The cell line SNU899 was provided by Dr. Kim CH of Ajou University. We used each HNSCC cell line within 3 months of purchase; cell lines used after 3 months of purchase were authenticated and characterized before use. CAL27 cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin (PS). FaDu cells were cultured in Eagle's Minimum Essential Medium (MEM) supplemented with 10% FBS and 1% PS. SCC25 and SCC9 cells were cultured in DMEM/F-12 supplemented with 10% FBS and 400 ng/mL hydrocortisone. All the other cell lines (HSC2, HSC3, HSC4, SNU1076, SNU1214, SNU46, SNU899, YD10B, YD38, and YD8) were cultured in RPMI supplemented with 10% FBS and 1% PS. The cultures were incubated in a 5% $CO_2$ incubator at 37°C.

### 2. Clonogenic survival assays

Exponentially growing cells were irradiated with 2 Gy radiation using a 250-kVp X-ray (0.61 Gy/min). Then, the irradiated cells were replated in a serum-containing medium at cloning densities. Cells were grown for 10 to 16 days, following which they were fixed and stained with Gentian violet. Colonies of more than 50 cells were scored. The same process was repeated three times for each cell line. The colony-forming efficiency of irradiated cells was determined, averaged, and normalized to that of non-irradiated control cells. The surviving fraction after 2 Gy of radiation (SF-2Gy) was calculated for all 14 cell lines.

### 3. Investigating RNA expression in cell lines using CCLE

RNA expression data of each HNSCC cell line was retrieved from the Cancer Cell Line Encyclopedia (CCLE) database (http:// www.broadinstitute.org/ccle) [16]. Gene expression data of about 18,361 genes was searched, log transformed, median centered, and scaled to the same minimum/maximum for each HNSCC cell line.

### 4. Identification of RSS

The survival fraction of 14 HNSCC cell lines after irradiation with 2 Gy radiation was assessed as described above, and four radioresistant cell lines showing high survival fraction values and four radiosensitive cell lines showing low survival fraction values were selected. Receiver operating characteristic (ROC) curve was generated by calculating sensitivity and specificity of expression of each gene in radioresistant and radiosensitive cell lines. Spearman correlation was used to determine the correlation of SF-2Gy with RNA expres-


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sion data of each HNSCC cell line obtained from the CCLE. Fold change was calculated for every gene between the 25th and 75th percentile of expression. RSS were selected if it satisfied all four inclusion criteria: (1) area under the ROC curve (AUC) ≥0.99, (2) fold change ≥4.3, (3) Spearman correlation R ≥0.6, and (4) Spearman correlation $p < 0.05$.

### 5. Patient cohort

This study analyzed the HNSCC cohorts from TCGA. Gene expression levels and clinical data of TCGA were downloaded from the UCSC Cancer Genomics Browser (https://xena.ucsc.edu/public). Patients with HPV(–) TCGA HNSCC who received adjuvant or definitive radiotherapy were selected for validation of radiosensitive genes obtained from HNSCC cell lines. The gene expression profile of TCGA HNSCC cohorts was measured experimentally using the Illumina HiSeq 2000 RNA Sequencing platform at the University of North Carolina TCGA genome characterization center. All the gene expression data of TCGA HNSCC cohorts was log transformed, median centered, and scaled to the same minimum/maximum as in the HNSCC cell lines to make the disparate platforms comparable.

### 6. Prediction, validation, and statistical analysis

Using data of eight HNSCC cell lines (four radioresistant and four radiosensitive cell lines) as a training set, class prediction procedure was carried out for patients with HPV(–) TCGA HNSCC using compound covariate predictor (CCP) class prediction engine [17,18] with leave-one-out cross-validation (BRB Array Tools) [19]. Genes significantly different between the classes at 0.99 significance level were used for class prediction. Only the genes with a fold-difference between the two classes exceeding 2 were used for class prediction. Then, patients with HPV(–) TCGA HNSCC were classified into radioresistant and radiosensitive groups. Recurrence-free survival (RFS) was defined as the number of months from the date of diagnosis to the event of recurrence [20]. We used Kaplan-Meier method to produce RFS curves in each group of the TCGA cohort. Then, log-rank test was used to compare the RFS between two groups. Univariate and multivariate Cox proportional hazards modeling was performed to evaluated independent prognostic factors associated with the recurrence of HPV(–) HNSCC. $p < 0.05$ was considered statistically significant. R software package (http://www.r-project.org) was used for all statistical analyses.

### 7. Pathway analysis

The identified RSS was analyzed by Qiagen's ingenuity pathway analysis (IPA) software program. At first, the identified RSS was uploaded into Qiagen's IPA system (http://www.ingenuity.com) for core analysis and then was overlaid with the global molecular network in the ingenuity pathway knowledge base (IPKB) [21]. IPA was performed to identify canonical pathways, upstream regulators, diseases and functions, and gene networks related to radiosensitive genes in HNSCC.

### 8. Research ethics

This study was approved by the Kyung Hee University Medical Center Institutional Review Board prior to its initiation (No. 2018-05-046).

## Results

### 1. Development of RSS

To develop radiosensitive genes in HNSCC, we investigated the SF-2Gy of 14 HNSCC cell lines. The SF-2Gy in each cell line ranged from 48% to 72% (Fig. 1A). Then, we identified four radioresistant (FaDu, SNU1076, YD38, HSC3) and four radiosensitive cell lines (SCC9, YD10B, HSC2, SCC25). The value of SF-2Gy was significantly higher in radioresistant cell lines than radiosensitive cell lines (62%–72% vs. 48%–51%; $p = 0.028$) (Fig. 1A).

Forty-one genes with significant correlation with SF-2Gy were identified in the radioresistant and radiosensitive cell lines through AUC, fold change, and Spearman correlation analysis (Fig. 1B). Of these, 6 genes were positively correlated and 35 genes were negatively correlated with radioresistance, respectively. A full list of these genes is depicted in Supplementary Table S1.

### 2. Prediction and validation of radiation sensitivity signature

The gene expression profiles and clinical data of patients with HPV(–) TCGA HNSCC who received adjuvant or definitive radiotherapy were used in this study ($n = 203$) (Table 1). Class prediction was applied to the data of patients with HPV(–) TCGA HNSCC using BRB Array Tools, following which the HPV(–) TCGA HNSCC cohorts were classified into radioresistant ($n = 149$) and radiosensitive ($n = 54$) groups (Fig. 2A). Five-year RFS rate was significantly lower in the radioresistant group than in the radiosensitive group (57.8% vs. 80.1%, respectively; $p = 0.035$). The corresponding Kaplan-Meier curves are presented in Fig. 2B.

In addition, univariate and multivariate Cox proportional hazards models including patients' demographics, social history, and clinical staging showed that only RSS is an independent prognostic factor of recurrence in patients with HPV(–) HNSCC who received adjuvant or definitive radiotherapy ($p < 0.05$) (Table 2).

### 3. Ingenuity pathway analysis

To identify canonical pathways, upstream regulators, diseases and

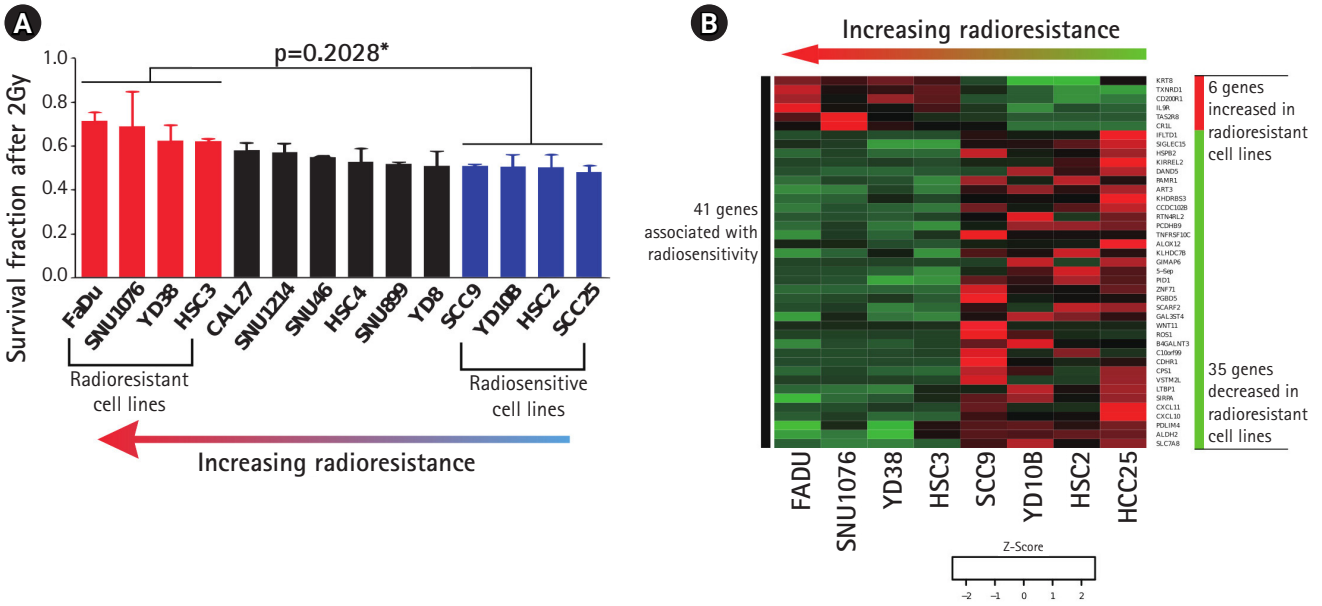


**Fig. 1.** Clonogenic survival assays performed to assess the surviving fraction after 2 Gy of radiation (SF-2Gy) identified the range of radioresistance in 14 HPV(–) HNSCC cell lines (48%–72%). (A) Four radioresistant cell lines and four radiosensitive cell lines were selected based on SF-2Gy in each HPV(–) HNSCC cell line (62%–72% vs. 48%–51%; p = 0.028). On comparison of the radioresistant and radiosensitive cell lines, 41 genes with significant correlation with radioresistance were identified; 6 genes were positively correlated with radioresistance and 35 genes were negatively correlated with radioresistance. (B) Relative gene expression levels of these 41 genes in the four radioresistant and four radiosensitive cell lines are depicted. HPV, human papillomavirus; HNSCC, head and neck squamous cell carcinoma.

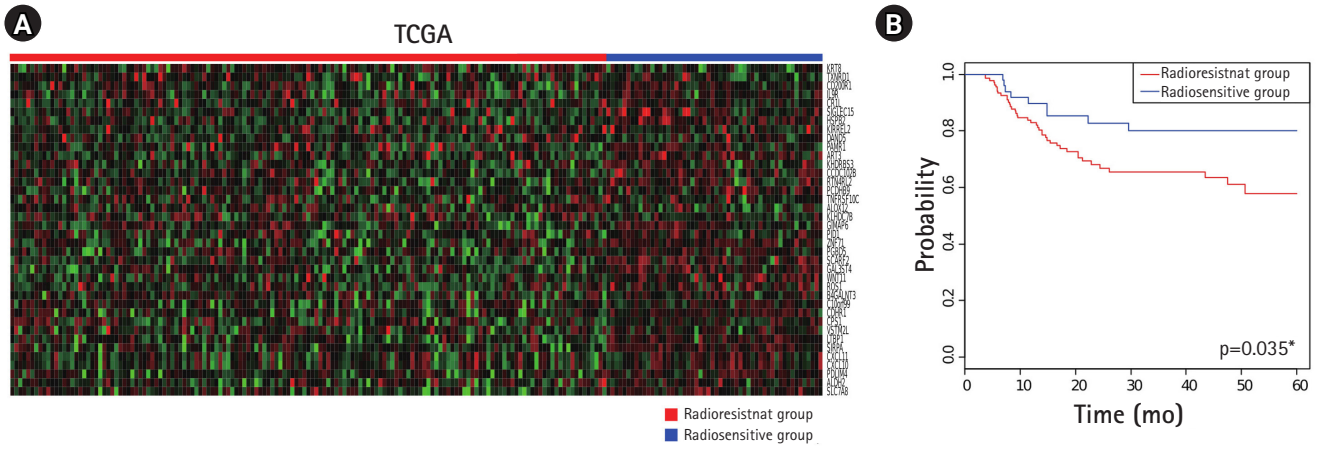


**Fig. 2.** Using four radioresistant and four radiosensitive cell lines with 41 genes significantly correlated with radioresistance as a training set, class prediction was carried out for patients with HPV(–) TCGA HNSCC who received adjuvant or definitive radiotherapy. (A) The patients with HPV(–) TCGA HNSCC were classified into radioresistant (n = 149) and radiosensitive (n = 54) groups. (B) Using Kaplan-Meier curves, 5-year RFS rate of each group was determined. The radioresistant group showed significantly lower 5-year RFS rate than the radiosensitive group (57.8% vs. 80.1%; p = 0.035). HPV, human papillomavirus; TCGA, The Cancer Genome Atlas; HNSCC, head and neck squamous cell carcinoma; RFS, recurrence-free survival.

functions, and gene networks related to radiosensitive genes in HNSCC, RSS was analyzed by Qiagen's IPA software program. The top canonical pathways, upstream regulators, molecular and cellular functions related to RSS are summarized in Table 3. PDE4B, LILRB4, RARRES3, IFNL4, and TICAM1 were found to be the top upstream regulators of RSS. Moreover, we found that cell death and survival, cell to cell signaling, and cellular movement were significantly enriched in the RSSs. To identify key genes involved in radiosensitivity in HPV(–) HNSCC and establish the connections in-between these genes, the gene network diagram was made based on

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**Table 1.** Patients' characteristics (n = 203)

| Characteristic | Number of patients (%) |
|---|---|
| Gender | |
| Male | 152 (74.9) |
| Female | 51 (25.1) |
| Age (yr) | |
| > 60 | 111 (54.7) |
| ≤ 60 | 92 (45.3) |
| Smoking | |
| Yes | 154 (77.4) |
| No | 45 (22.6) |
| Unknown | 4 (2.0) |
| Alcohol | |
| Yes | 142 (70.0) |
| No | 60 (29.6) |
| Unknown | 1 (0.5) |
| Tumor site | |
| Oral cavity | 137 (67.5) |
| Oropharynx | 3 (1.5) |
| Hypopharynx | 4 (2.0) |
| Larynx | 59 (29.1) |
| Primary tumor | |
| T1-T2 | 47 (24.1) |
| T3-T4 | 132 (67.7) |
| Unknown | 16 (8.2) |
| Lymph node metastasis | |
| Negative | 61 (30.0) |
| Positive | 113 (55.7) |
| Unknown | 29 (14.3) |
| Stage | |
| I-II | 20 (9.8) |
| III-IV | 176 (86.7) |
| Unknown | 7 (3.4) |
| Treatment type | |
| Radiotherapy only | 13 (6.4) |
| Operation + Radiotherapy | 165 (81.3) |
| Operation + Chemoradiotherapy | 24 (11.8) |
| Chemoradiotherapy | 1 (0.5) |

IPKB and is depicted in Fig. 3. The gene network diagram showed that RSSs were highly correlated with each other.

## Discussion and Conclusion

In this study, we developed a molecular biomarker signature of radiation response in HPV(–) HNSCC using various HNSCC cell lines.

**Table 3.** Top canonical pathways, upstream regulators, molecular and cellular functions related to radiation sensitivity signature

| | p-value | p-value (range) |
|---|---|---|
| Top canonical pathways | | |
| Pathogenesis of multiple sclerosis | $1.35 \times 10^{-4}$ | |
| IL-17A signaling in gastric cells | $1.10 \times 10^{-3}$ | |
| Granulocyte adhesion and diapedesis | $4.17 \times 10^{-3}$ | |
| Agranulocyte adhesion and diapedesis | $4.99 \times 10^{-3}$ | |
| Phenylethylamine degradation I | $7.85 \times 10^{-3}$ | |
| Top upstream regulators | | |
| PDE4B | $5.40 \times 10^{-5}$ | |
| LILRB4 | $7.55 \times 10^{-5}$ | |
| RARRES3 | $1.01 \times 10^{-4}$ | |
| IFNL4 | $1.61 \times 10^{-4}$ | |
| TICAM1 | $2.36 \times 10^{-4}$ | |
| Top molecular and cellular functions (related molecules) | | |
| Cellular movement (9) | | $5.00 \times 10^{-2}$ to $1.13 \times 10^{-5}$ |
| Cell death and survival (15) | | $3.02 \times 10^{-2}$ to $2.26 \times 10^{-5}$ |
| Amino acid metabolism (3) | | $3.74 \times 10^{-2}$ to $1.97 \times 10^{-3}$ |
| Cell morphology (4) | | $4.62 \times 10^{-2}$ to $1.97 \times 10^{-3}$ |
| Cell to cell signaling and interaction (10) | | $4.62 \times 10^{-2}$ to $1.97 \times 10^{-3}$ |

**Table 2.** Univariate and multivariate analysis of factors associated with recurrence-free survival in HPV(–) head and neck squamous cell carcinoma patients who received adjuvant or definitive radiotherapy

| Characteristic | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Radiation sensitivity signature | 0.460 (0.223–0.947) | 0.035* | 0.386 (0.166–0.893) | 0.026* |
| Gender (male) | 1.225 (0.613–2.446) | 0.566 | 0.981 (0.451–2.131) | 0.961 |
| Age (> 60 yr) | 1.028 (0.591–1.784) | 0.923 | 1.293 (0.692–2.417) | 0.419 |
| Smoking (yes) | 0.990 (0.518–1.894) | 0.978 | 0.879 (0.423–1.829) | 0.731 |
| Alcohol (yes) | 1.459 (0.763–2.787) | 0.253 | 1.423 (0.673–3.009) | 0.355 |
| Primary tumor (T3 & T4) | 0.980 (0.515–1.863) | 0.952 | 1.037 (0.450–2.386) | 0.931 |
| Regional lymph node (N+) | 1.192 (0.643–2.209) | 0.577 | 1.432 (0.731–2.806) | 0.294 |
| Stage (stage III & IV) | 1.014 (0.401–2.560) | 0.977 | 0.516 (0.152–1.748) | 0.288 |

HPV, human papillomavirus; HR, hazard ratio; CI, confidence interval.
*$p < 0.05$.

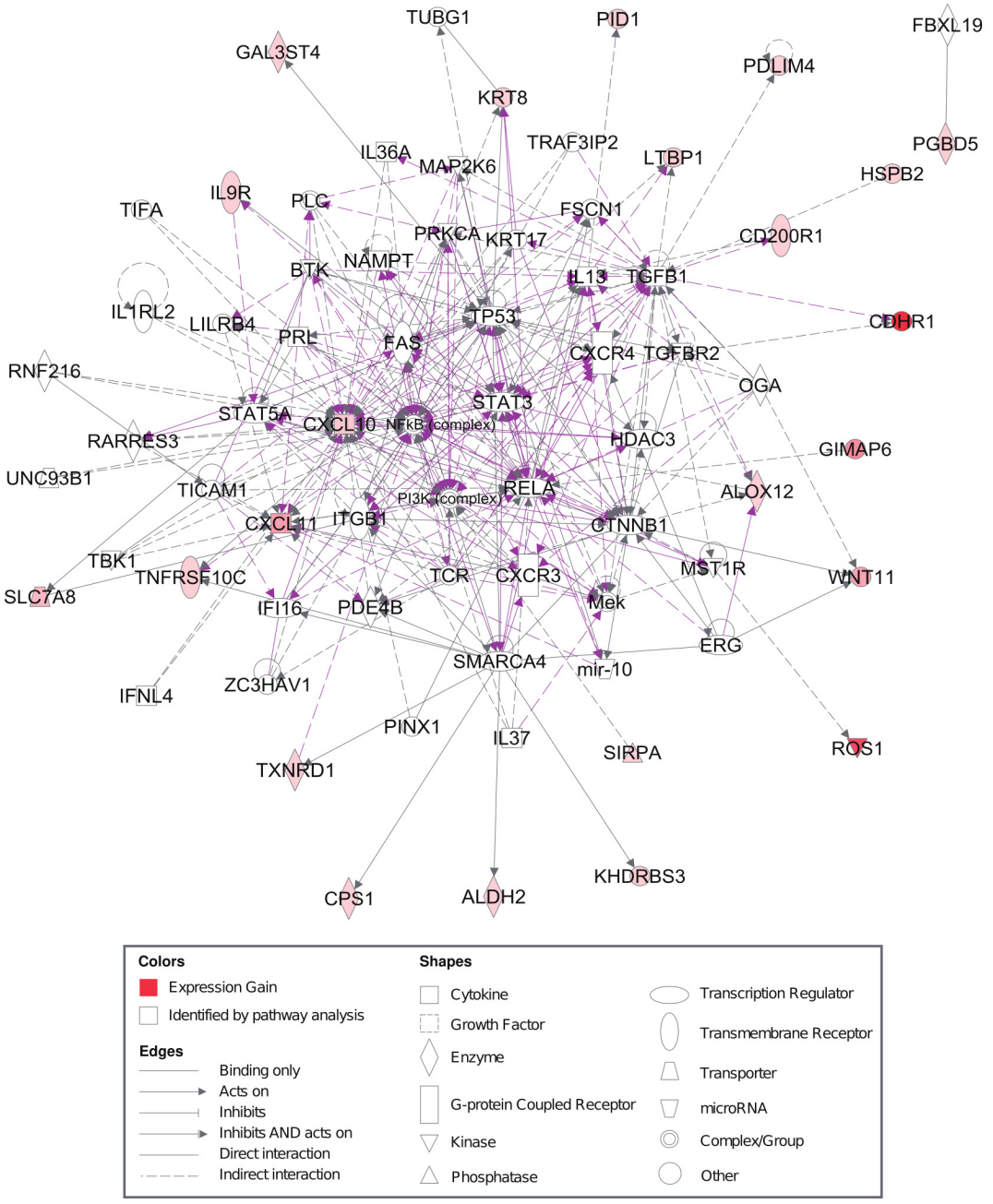


**Fig. 3.** Gene network diagram based on ingenuity pathway analysis showing connections in-between radiation sensitivity signatures.

We classified independent HPV(–) TCGA HNSCC cohort into radioresistant and radiosensitive groups based on RSS. Recurrence after adjuvant or definitive radiotherapy was significantly lower in the radiosensitive group than in the radioresistant group. Thus, RSS in HPV(–) HNSCC may have the ability to identify patients with HNSCC who are refractory to adjuvant or definitive radiotherapy and need treatment intensification or personalized treatment. These RSSs showed various interactive pathways and networks related to cellular movement, cell death and survival, amino acid metabolism, cell morphology, and cell-to-cell signaling.

We used various HPV(–) HNSCC cell lines to include each subsite of HNSCC such as oral cavity, pharynx, supraglottis, glottis, and subglottis in the study. In addition, standard fractionation (2 Gy) was applied to the HNSCC cell lines to evaluate each surviving fraction after irradiation. The mRNA expression levels of each HNSCC cell line were obtained from the CCLE database (http://www.broadinstitute.org/ccle), because CCLE may provide representative genetic proxies for primary tumors in many cancer types [22].

Moreover, an enormous amount of biological and clinical data—big data—facilitated us to validate RSSs from the HNSCC cell lines.


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TCGA is the largest dataset and contains measurements of somatic mutations (sequencing), copy number variations (array based and sequencing), mRNA expression (array based and sequencing), miRNA expression (array based and sequencing), protein expression (array based), and histology slides for approximately 7,000 human tumors (http://cancergenome.nih.gov/). Here, from the clinical data of 604 TCGA HNSCC patients, the data of 203 patients with HPV(–) TCGA HNSCC who received radiotherapy was selected for validation.

We could interpret the gene expression profiles using advanced bioinformatic analysis as revealed by microarray. In this study, we used the IPA software program—one of the advanced bioinformatic analysis tools—which can analyze the gene expression patterns using a built-in scientific literature based database (www.ingenuity.com) [21]. IPA results helped us in finding cellular functions and several pathways and networks related to RSS. It has been reported that five top upstream regulators, namely, PDE4B, LILRB4, RARRES3, IFNL4, TICAM1, are associated with colorectal cancer [23], leukemia [24], breast cancer [25], prostate cancer [26], and thyroid cancer [27], respectively. These regulators seem to be associated with radiosensitivity in some ways. The levels of intracellular cAMP, which is a well-characterized secondary messenger that elicits a wide range of cellular processes including proliferation, differentiation, migration, growth, and apoptosis, are regulated by the activities of two enzymes, adenylyl cyclase and phosphodiesterase including PDE4B [23]. Appukuttan et al. [28] found that inhibition of soluble adenylyl cyclase had increased the radiosensitivity of prostate cancer cells. Interferon-related DNA damage resistance signature (IRDS) induced by all interferon including IFNL4 showed effects leading to resistance to ionizing radiation [26]. Association between T lymphocyte and other regulators such as LILRB4, TICAM1 had been reported [24,29]. These regulators are not RSSs of HPV(–) HNSCC, but needed to be further investigated for their association with HNSCC and radiotherapy. In addition, various molecular and cellular functions were enriched in the RSS of

HPV(–) HNSCC and gene network framework showed that the RSSs were highly correlated with each other in a complex manner.

Recently, some studies have investigated the correlation of genetic mechanisms and treatment response including radiotherapy in patients with HNSCC. MRP2 and RB were found to be associated with the outcome of concurrent chemoradiation in patients with HNSCC [12]. Additionally, the expression levels of cancer stem cell markers CD44, SLC3A2, and MET were correlated with tumor recurrence in HPV(–) HNSCC after postoperative chemoradiation [13]. Several hallmarks including EMT which refers to a process whereby the adhesive polarity of epithelial cancer cells dissipates and changes to mesenchymal cells, angiogenesis, and DNA repair were significantly correlated with 13 radioresistance-associated genes [14]. In a recent study, a seven-gene signature predicting recurrence in patients with locally advanced HNSCC treated with postoperative radiotherapy or radiochemotherapy was developed and validated [8]. These results were developed from gene sets well known for their role in biological or cancer metabolism such as DNA repair, cancer stem cells, chemoresistance, HPV association, hypoxia, proliferation, etc. Conversely, this study developed several novel RSSs from HNSCC cell lines using CCLE regardless of the role of the genes.

There had been also some reports showing association between the RSSs and radiosensitivity. TXNRD1, which was significantly increased in radioresistant group, encodes thioredoxin reductase 1 (TrxR1). Several studies reported that specific inhibition of TrxR1 increased radiosensitivity via enhancement ROS levels [30-32]. Luo et al. [33] found that *PDLIM4* gene was involved in radioresistance of glioma cells. PDLIM4 necessary for dendritic cell migration via CCR7-JNK, dendrite formation, and subsequent development of functional T-cell responses was inactivated in multiple cancer types [34]. ALDH2 detoxifies toxic aldehydes formed by accumulated reactive oxygen resulted from ionizing radiation. Ning et al. [35] reported that reactive aldehydes played an important role in the intrinsic radiosensitivity of normal and tumor tissue. The chemokine CXCL10 plays a role in angiostasis and has anti-tumor effects. It was reported that high expression of CXCL10 was related to better response to neoadjuvant chemoradiotherapy as well as improved survival in colorectal cancer patients [36,37]. Lukas et al. [38] found that a young woman with ROS1 oncogene rearranged non-small cell lung cancer (NSCLC) with brain metastases was sensitive to radiotherapy. PDLIM4, ALDH2, CXCL10, and ROS1 were significantly decreased in radioresistant group. However, there are still many RSSs that need to be investigated for their association with radiosensitivity in carcinoma, especially HNSCC.

Our study showed that only RSS was an independent prognostic factor of RFS in patients with HPV(–) TCGA HNSCC who received adjuvant or definitive radiotherapy. Clinical tumor stage was not prognostic factor in TCGA dataset. Most patients (n = 176) were diagnosed with advanced stage and only 20 patients were diagnosed with early stage, because early stage patients requiring only surgical therapy were excluded in this study. Also, among 20 early stage patients, 11 patients received operation with radiotherapy, and 3 patients received operation with chemoradiotherapy. In other words, most patients in early stage needed additional therapy, maybe because of their relative advanced state. We think these characteristics might influence the RFS in patients with HPV(–) HNSCC who received adjuvant or definitive radiotherapy.

Our study has the following limitations. First, the subsites of HN-

SCC cell lines are diverse and include oral cavity, pharynx, and larynx. Thus, diverse radiation sensitivity of each subsite might have been overlooked. However, we focused on overall HPV(–) HNSCC which has poor prognosis than HPV(+) HNSCC. Second, we did not isolate RNA from the HNSCC cell lines, but used mRNA expression data from CCLE. Since CCLE might provide data with genomic similarities to primary tumors [22], we used HNSCC cell lines within three months of purchase or used them after authentication. Finally, little is known about the RSSs developed in this study. Further experiments including IPA described above are needed to comprehend the underlying molecular mechanism of each RSS.

Nevertheless, as far as we know, this is the first study to identify RSSs associated with HPV(–) HNSCC from gene database of various HNSCC cell lines. We investigated patients with HPV(–) HNSCC treated by adjuvant or definitive radiotherapy irrespective of operation, focusing on their prognosis that is worse than that in patients with HPV(+) HNSCC. In addition, RSSs were validated using big data—patients with HPV(–) TCGA HNSCC treated by radiotherapy. It means that our validation results for RSSs might be influenced by minimal selective error and could be reproducible. Furthermore, Cox proportional hazards model showed that only RSS is the independent prognostic factor influencing recurrence of HPV(–) HNSCC in patients after radiotherapy. As each patient had HNSCC at a different clinical stage and was treated with different amount of radiation dose, a direct comparison between radioresistant and radiosensitive groups might be impractical. However, the sole prognostic factor, RSS, needs to be noted and further investigated.

In conclusion, we derived 41 RSSs that could predict recurrence in HPV(–) HNSCC. The outcome of adjuvant or definitive radiotherapy in HPV(–) HNSCC can be predicted by analyzing the expression of RSSs. Further validation of RSS according to each subsite of HNSCC in other HNSCC cohorts may facilitate the application of RSSs in treatment. In other words, personalized treatment plan for treatment of HPV(–) HNSCC could be established by further organization and stratification of RSSs.

## Conflict of Interest

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

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## Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2020.00136.

Table S1. Genes correlated with survival fraction after 2-Gy radiation in HPV-negative head and neck squamous cell carcinoma cell lines.

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# Late-term effects of hypofractionated chest wall and regional nodal radiotherapy with two-dimensional technique in patients with breast cancer

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**Purpose:** Hypofractionated radiotherapy (RT) is becoming a new standard in postoperative treatment of patients with early stage breast cancer after breast conservation surgery. However, data on hypofractionation in patients with advanced stage disease who undergo mastectomy followed by local and regional nodal irradiation (RNI) is lacking. In this retrospective study, we report late-term effects of 3 weeks post-mastectomy hypofractionated local and RNI with two-dimensional (2D) technique in patients with stage II and III breast cancer.

**Methods:** Between January 1990 and December 2007, 1,770 women with breast cancer who were given radical treatment with mastectomy, systemic therapy and RT at least 10 years ago were included. RT dose was 35 Gy/15 fractions/3 weeks to chest wall by two tangential fields and 40 Gy in same fractions to supraclavicular fossa (SCF) and internal mammary nodes (IMNs). SCF and IMNs dose was prescribed at $d_{max}$ and 3 cm depth, respectively. Chemotherapy and hormonal therapy was given in 64% and 74% patients, respectively. Late-term toxicities were assessed with the Radiation Therapy Oncology Group (RTOG) scores and LENT-SOMA scales (the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic scales).

**Results:** Mean age was 48 years (range, 19 to 75 years). Median follow-up was 12 years (range, 10 to 27 years). Moderate/marked arm/shoulder pain was reported by 254 (14.3%) patients. Moderate/marked shoulder stiffness was reported by 219 (12.3%) patients. Moderate/marked arm edema was seen in 131 (7.4%) patients. Brachial plexopathy was not seen in any patient. Rib fractures were noted in 6 (0.3%) patients. Late cardiac and lung toxicity was seen in 29 (1.6%) and 23 (1.3%) patients, respectively. Second malignancy developed in 105 (5.9%) patients.

**Conclusion:** RNI with 40 Gy/15 fractions/3 weeks hypofractionation with 2D technique seems safe and comparable to historical data of conventional fractionation (ClinicalTrial.gov Registration No. NCT04175821).

**Keywords:** Breast cancer, Hypofractionation, Radiotherapy, Long-term effects, Postmastectomy

## Introduction

Survival of breast cancer patients has improved with multimodality treatment [1]. Hypofractionated radiotherapy (RT) is rapidly emerging as one of the options for breast cancer patients after breast-conserving surgery (BCS) [2-4] but data on postmastectomy radiation therapy (PMRT) with hypofractionation is lacking. There is always a concern for late effects of RT especially with re-

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gional nodal irradiation (RNI). The potential survival benefit of locoregional radiation needs to be balanced with late-term effects [5]. Therefore, reporting late-term effects of radiation in these patients is of utmost importance, especially with hypofractionation. Very few patients were given PMRT and RNI in the START trials, so it may not be possible to establish the safety of shorter fractionation RNI from these studies [2-4]. Recently, a randomised study was done by Wang et al. [6] in high risk patients after mastectomy. At 5 years, they reported similar clinical outcomes and late toxicities with conventional and hypofractionation [6]. There are a few studies from Canada and the United States with similar dose fractionations in PMRT setting with small number of patients but without RNI [7,8]. So, there is a worldwide need of data on PMRT and RNI to establish its long-term safety in patients with breast cancer. Because of this, many radiation oncology societies are hesitant to recommend hypofractionated RNI. It is also an area for potential research in breast cancer radiotherapy. We have published our clinical outcomes with 3 weeks of postoperative local and RNI with hypofractionation in breast cancer in the past [9-13]. In this retrospective study, we report late-term effects of PMRT and RNI with this schedule in patients with stage II and III breast cancer treated with two-dimensional (2D) technique from a regional cancer centre in XXXX which is practicing hypofractionation in breast cancer since 1976.

## Materials and Methods

Between January 1990 and December 2007, women with breast cancer who were given radical treatment with mastectomy, systemic therapy and RT at least 10 years ago were included. Eligible patients were followed in the radiation oncology department breast clinic. The study was approved by the departmental committee and registered in ClinicalTrials.gov with No. NCT04175821. Clinical, pathological and treatment characteristics were taken from the patient's file. Inclusion criteria were female patients age ≥18 years of age, with invasive carcinoma of the breast, postmastectomy, and stage II or III disease treated with locoregional RT. Exclusion criteria were: BCS, stage I or IV disease, past history of malignancy except (1) basal cell skin cancer or cervical intraepithelial neoplasia (CIN) cervix uteri or (2) non-breast malignancy if treated with curative intent and at least 5 years disease-free or contralateral breast cancer, including ductal carcinoma *in situ* (DCIS), irrespective of date of diagnosis. Patients with bilateral breast cancer were also excluded.

All patients were planned in supine position on a breast board with ipsilateral arm abducted to 90° using 2D fluoroscopic conventional simulator. Chest wall was treated by two tangential fields. Field marking for breast/chest wall included midline medially, midaxillary fold laterally, 2nd intercostal space cranially and 1cm below the opposite inframammary fold caudally. Central lung distance (CLD) was noted for each patient (Fig. 1A). Supraclavicular fossa (SCF) was treated by a single incident field. Its caudal border was the cranial border of the chest wall field, cranially thyroid notch, medially along the medial border of the sternocleidomastoid muscle

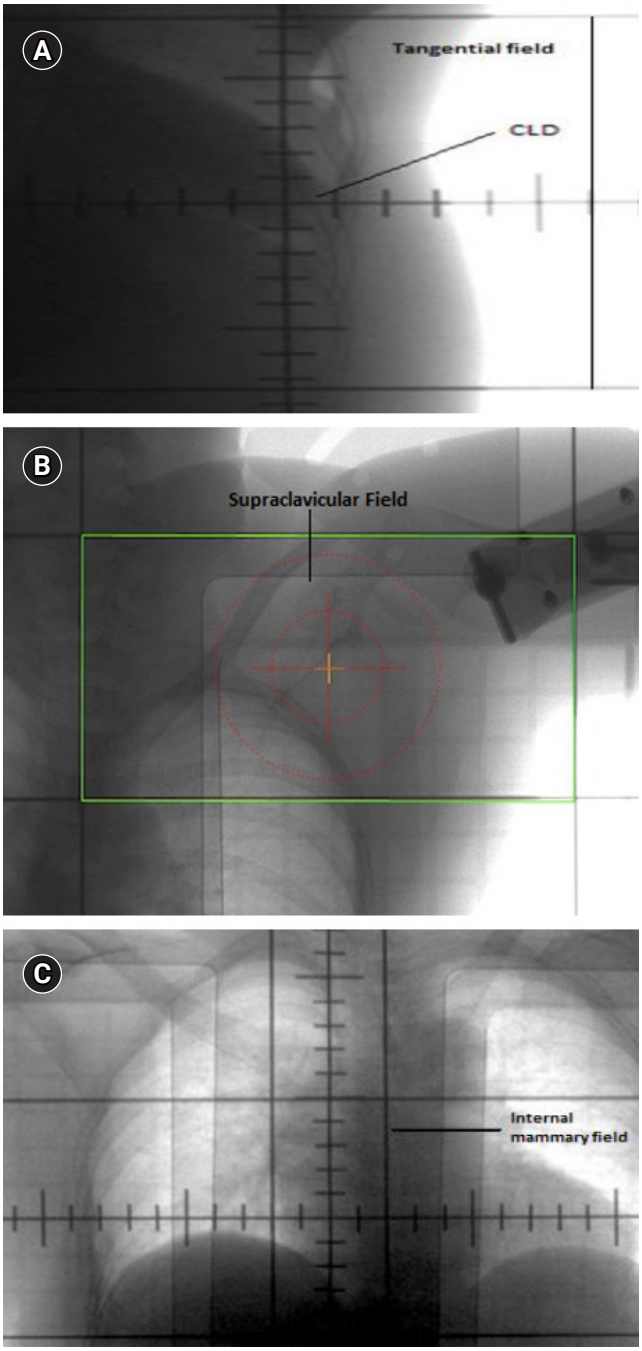


**Fig. 1.** (A) Tangetial field portal with central lung distance (CLD). (B) Supraclavicular field portal. (C) Internal mammary field portal.


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and laterally insertion of deltoid (Fig. 1B). No posterior axillary field was used. The head of the humerus was shielded in patients with adequate axillary dissection with <25% nodes involved.

RT dose delivered was 35 Gy/15 fractions (fx)/3 weeks to the chest wall. Dose was prescribed at mid-separation. Bolus was used in all patients on alternate days that is for 50% of treatment. In patients with positive margins bolus was used daily and a scar boost of 10–15 Gy/4–5 fx was given. None of the patients had breast reconstruction. The breast cone was used in patients treated on cobalt, which had a shielding block to reduce penumbra and lung dose.

Internal mammary nodes (IMNs) were irradiated with a separate $12 \times 5$ $cm^2$ single field (Fig. 1C). The first five intercostal spaces were included in the IMN target volume. The medial border of the IMN field was midline; lateral border 5 cm lateral to the midline; the superior border abuts the inferior border of the supraclavicular field; and the inferior border was above the xiphoid [9]. The dose delivered was 40 Gy/15 fx/3 weeks prescribed at 3 cm depth. SCF was treated with a single field and dose was prescribed at $d_{max}$. Patients were treated on linear accelerator (LINAC) or cobalt-60 machine.

Biologically effective dose (BED) of 35 Gy/15 fx/ 3 weeks is 62.2 $Gy_3$ in terms of 2 Gy per fraction for late effects, 43.17 $Gy_{10}$ for tumour control, 45 Gy for erythema and 42.3 Gy for desquamation in case of chest wall radiotherapy. The BED for RNI with this schedule is 75.47 $Gy_3$, 50.64 $Gy_{10}$, 52.5 Gy and 49 Gy for late effects, tumour control, erythema, and desquamation, respectively.

Dosimetric study was also done in 50 patients with left side breast cancer. Patients were planned on a 2D simulator on breast board. Field borders were set as described above and CLD was calculated. Field borders were marked. After that patients were taken to computed tomography (CT)-simulator for 3D treatment planning. The patients were positioned supine on same breast board in same position with same parameters as were on 2D simulator. Lead wires were placed on the field borders of chest wall and 100 mL of intravenous (IV) contrast was given. CT axial cuts were taken from the level of larynx to upper abdomen, including both the lungs with a scan thickness and index of 3 mm. Then, the CT images were transferred to the treatment planning system. The chest wall, heart, bilateral lungs, left anterior descending (LAD) artery, and opposite breast were contoured. A CT-based 3D planning was generated form the 2D marked target area for treating chest and locoregional lymph nodes (Fig. 2A). Plans were made using standard tangent fields. Heart, bilateral lungs, LAD artery, and opposite breast dose-volume histogram (Fig. 2B) were generated to see how much dose was received by organs-at-risk. From these, estimate of mean doses to heart, LAD, proximal LAD, distal LAD, bilateral lungs and opposite breast, $V_5$ of right lung, $V_5$, $V_{10}$, and $V_{20}$ of left lung and $V_2$ opposite breast were calculated. Treatment was done with 2D technique.

Patients were followed regularly 3 monthly during first year, 4 monthly in the second and third year, 6 monthly till 5 years, yearly till 10 years and 2 yearly thereafter. Necessary investigations were done to pick up the recurrence/metastasis and late toxicities depending on the symptoms of the patients.

Patients were examined by the radiation oncologists with special focus on shoulder function, lymphedema, arm pain, and sensory symptoms. Lymphedema was graded by measuring arm circumference 10 cm above and below the medial epicondyle of humerus. For lymphedema and shoulder function, the treated side was compared with the untreated opposite side as a reference. Lymphedema was classified as none, mild, moderate and marked if there was no difference, 0.5–2 cm, 2.1–3 cm, and >3 cm difference, respectively in the circumference of the affected and normal arm. If the patient had symptoms of pain in the arm, paresthesia, numbness, weakness, or other sensory symptoms then injury to the brachial plexus was suspected and reported as brachial plexopathy. Late lung toxicity was defined grade 1 as asymptomatic or mild symptoms of dry cough, slight radiographic changes; grade 2 as moderate symptomatic fibrosis or pneumonitis (severe cough), low grade fever, patchy radiographic changes; grade 3 as severe symptomatic fibrosis or pneumonitis, dense radiographic changes; and grade 4 as severe respiratory insufficiencies, oxygen required of assisted ventilation. Late cardiac toxicity was defined grade 1 as minimal enlargement of cardiac silhouette (ECS); grade 2 as ECS without pulmonary congestion; grade 3 as ECS pulmonary congestion; and grade 4 as ECS with frank pulmonary oedema. All late effects assessment scores were dichotomised as none/mild versus moderate/marked effects. Coronary events were defined as myocardial infarction, ischaemic heart failure, unstable angina or sudden death. A four point scale (none, a little, quite a bit, very much) was used to assess all late effects according to the LENT-SOMA scale. All late effects assessment scores were dichotomised as none/mild versus moderate/marked effects. Second malignancy was defined as cancer developing after 6 months of treatment of breast cancer except basal cell carcinoma of the skin and carcinoma *in situ* of cervix.

## Results

### 1. Patient and tumour characteristics

A total 1,770 patients met the eligibility criteria. Mean age was 48 years (range, 19 to 75 years). The median follow-up was 12 years (range, 10 to 27 years). Characteristics of patients are as shown in Table 1.

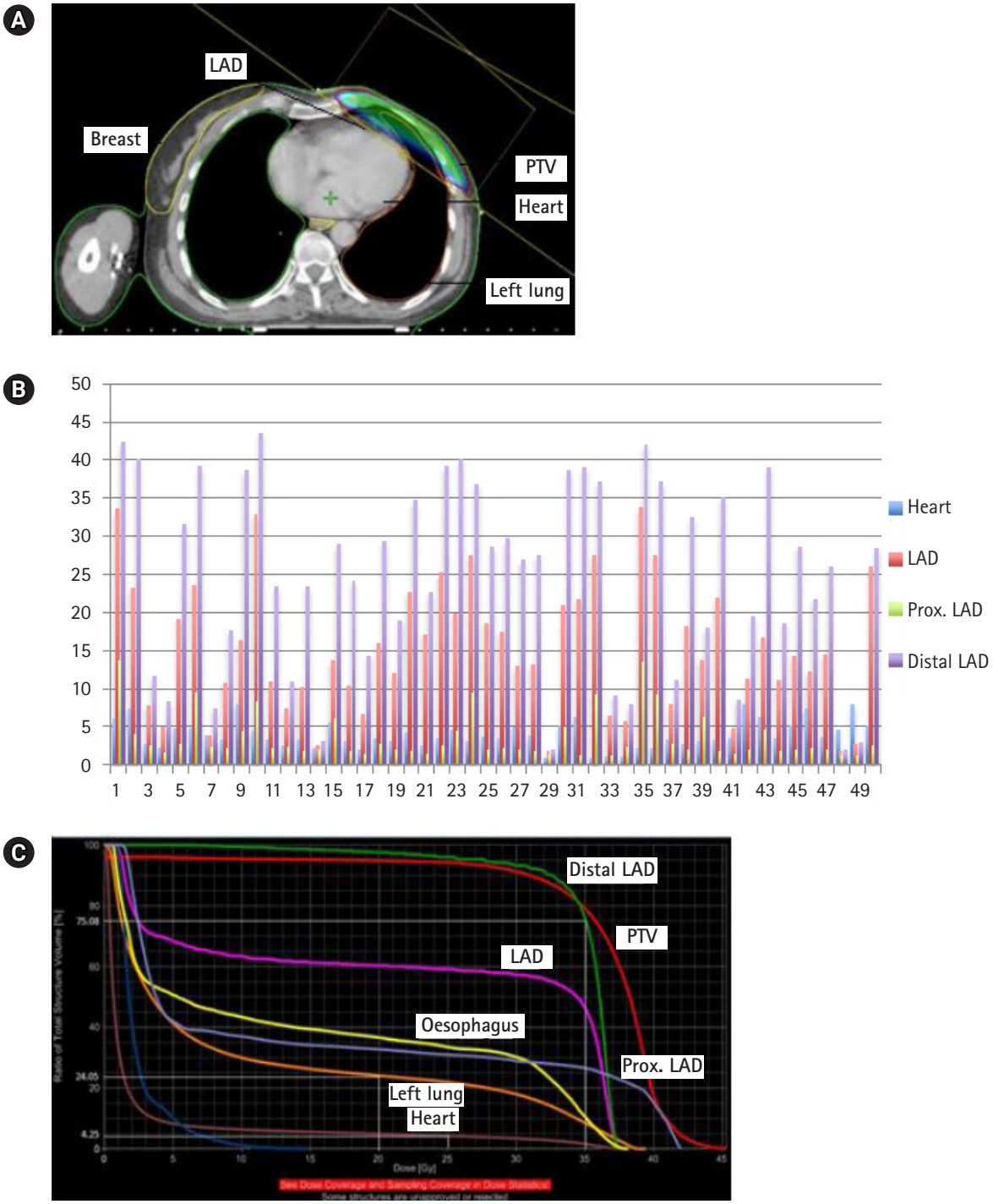


**Fig. 2.** (A) Organs-at-risk (OARs) and planning target volume (PTV) covered by 95% isodose. (B) Mean doses to OARs (dose along y-axis and patients along x-axis). (C) Dose volume histogram showing dose to PTV and OARs. LAD, left anterior descending; Prox, proximal.

## 2. Treatments received

Surgery was modified radical mastectomy and total mastectomy with axillary clearance in 762 (43%) and 1,008 (57%) patients, respectively. Median number of axillary nodes dissected were 10. Chemotherapy was given to 1,136 (64%) patients. Chemotherapy regimens included CMF (cyclophosphamide, methotrexate and 5-fluorouracil), anthracycline, and anthracyclines and taxane-based chemotherapy in 443 (39%), 455 (40%), and 240 (21%) patients, respectively. Hormonal therapy was given to 1,310 (74%) patients.

Right and left chest wall was irradiated in 973 (55%) and 797 (45%) patients, respectively. RNI was delivered in 1,689 (95%) pa-


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**Table 1.** Patient characteristics (n = 1,770)

| Characteristic | Value |
|---|---|
| Age (yr) | |
| ≤ 40 | 491 (28) |
| > 40 | 1,279 (72) |
| Laterality | |
| Right | 973 (55) |
| Left | 797 (45) |
| Menopausal status | |
| Pre-menopausal | 828 (47) |
| Post-menopausal | 942 (53) |
| Tumor stage | |
| T1 | 906 (51) |
| T2 | 659 (37) |
| T3 | 34 (2) |
| T4 | 171 (10) |
| Histology | |
| IDC | 1,628 (92) |
| Non-IDC | 142 (8) |
| Grade | |
| 1 | 318 (18) |
| 2 | 1,134 (64) |
| 3 | 318 (18) |
| N stage (pathological) | |
| pN0 | 654 (37) |
| pN1 | 593 (34) |
| pN2 | 383 (22) |
| pN3 | 140 (8) |
| Surgical margins | |
| Negative | 1,562 (88) |
| Positive | 208 (12) |
| Estrogen receptor status | |
| Positive | 859 (49) |
| Negative | 530 (30) |
| Unknown | 381(21) |
| Progesterone receptor status | |
| Positive | 729 (41) |
| Negative | 632 (36) |
| Unknown | 409 (23) |
| Chemotherapy | |
| Yes | 1,136 (64) |
| No | 634 (36) |
| Hormonal therapy | |
| Yes | 1,310 (74) |
| No | 460 (26) |

Values are presented as number of patients (%).
IDC, invasive ductal carcinoma.

tients. Internal mammary nodal irradiation (IMNI) was delivered in 154 (9%) patients. Average CLD was 2 cm (range, 1 to 3 cm). In 50 patients with left breast cancer in whom dosimetry was done their dosimetric data is shown in Fig. 2B. Mean doses to the heart, LAD, proximal LAD, and distal LAD were 3.364 Gy, 16.06 Gy, 2.7 Gy, and 27.5 Gy, respectively. Left lung mean dose, $V_5$, $V_{10}$, and $V_{20}$ were 5.96 Gy, 16%, 14%, and 12.4%, respectively. Mean dose to the right lung and the opposite breast was 0.29 Gy and 0.54 Gy, respectively. DVH is shown in Fig. 2C. $V_{25}$ for heart was 4.25% where as $V_{35}$ for distal LAD was 75% as compared to 26% for distal LAD. V30 for the oesophagus was 30%.

## 3. Toxicities

Late toxicity rates are summarized in Table 2. Moderate/marked arm/shoulder pain was reported by 254 patients (14.3%; 95% confidence interval [CI], 12.7–16.1). Moderate/marked shoulder stiffness reported by 219 patients (12.3%; 95% CI, 10.9–14.0). Arm oedema developed in 131 patients (7.4%; 95% CI, 6.2–8.7). Lymphedema rate significantly increased with the number of axillary lymph nodes dissected (Table 3). It was 4.9%, 9%, and 12.6% in patients with ≤ 10, 11–20, and > 20 axillary lymph nodes dissected, respectively.

Brachial plexopathy was not seen in any of the patients. Arm/shoulder pain and stiffness decreased at 10 and 15 years. Arm edema rate was similar at 5, 10, and 15 years. Late grade III cardiac toxicity was seen in 29 patients (1.6%; 95% CI, 1.1–2.3). Coronary events were reported in 7 patients (0.3%; 95% CI, 0.1–0.7). Coronary bypass surgery and stent placement was done in 3 patients each. Pacemaker was inserted in one patient. Four of these had received IMNI, 3 for left and 1 for right breast cancer, respectively. Late grade III lung toxicity (on the treated side) was seen in 23 patients (1.3%; 95% CI, 0.8–1.9) (Table 2). Lung and cardiac toxicities were constant at 10 and 15 years. Rib fractures were noted in 6 patients (0.3%; 95% CI, 0.1–0.7) on the treated side. There was no association between the dosimetric factors and lung and heart toxicities in these patients.

Second malignancy developed in 105 patients (5.9%; 95% CI, 4.9–7.1). Most common site of second malignancy was opposite breast in 61 (3.3%) patients. Non-breast second malignancy developed in 44 (2.3%) patients. Most common non-breast second malignancy was gynaecological 25 (1.3%); 6, 8, and 11 in cervix, endometrium, and ovary, respectively. Gastrointestinal tract 9 (0.5%); 4 in oesophagus (radiation related), 3 colon, 1 stomach, 1 gall bladder, and 1 rectum. Haematological, thyroid (radiation related), and renal 2 (0.1%) each. Others were carcinoma of lung (on the untreated side), vallecula and liposarcoma (on the treated side) one each. Rate of second malignancies increased over 5, 10, and 15 years (Table 2).

## Discussion and Conclusion

In the present study, late-term toxicities were modest following 3 weeks postmastectomy hypofractionated locoregional RT. Our findings suggest that RNI with hypofractionation may be as safe as conventional fractionation.

This is a large study on postmastectomy hypofractionated regional RT with long-term follow-up reporting late-term effects in patients with breast cancer. Our results indicate that arm and shoulder functions improved over the years (Table 2). The START trials also reported late effects after hypofractionated PMRT and RNI [2-4]. RNI to the axilla and SCF was given in 58 (15.1%), 24 (7.6%), and 15 (9.3%) patients in START-pilot, START-A, and START-B trials, respectively. Dose fractionation used was different in all the trials. Patient population in these trials was also heterogeneous in term of extent of axillary dissection, RNI, radiation dose, technique and adjuvant systemic treatment. IMNI was not delivered in these trials. Finally these patients may not be representative of global population because of ethnicity and anthropometry variation. Patients included in START trials were > 50 years of age and early stage. We have included young as well as elderly and advanced stage patients in the present study. The argument here might be slight lower PMRT dose of 35 Gy in our study as compared to 40 Gy in START trials, but our results in terms of local control [8-12] are comparable to START trials. This dose is also similar to UK IMPORT Low trial. However, the dose delivered to the axilla and SCF in the present study was same as in START B trial, i.e., 40 Gy in 15 fractions, the equivalent dose in 2 Gy ($EQD_{2Gy}$) of which is 46 Gy and 48 Gy assuming $\alpha/\beta$ values of 3 Gy and 1.5 Gy, respectively.

In a recent well-designed randomised study by Wang et al. [6], they concluded that 3-week hypofractionation was non-inferior to conventional fractionation in terms of efficacy and safety. They reported similar clinical outcomes and toxicities between the two arms [6]. This study also established the safety of RNI in patients with breast cancer. They reported lymphedema rate of 19% at 5 years which is comparable to 7% in the current study. Shoulder dysfunction of 8.8% in our study is slightly higher than that reported by Wang et al. [6] of 3%. Our results in terms of lung and cardiac toxicities are also comparable to the hypofractionated arm of the study reported by Wang et al. [6]. They reported < 1% grade 3 lung and cardiac toxicities at 5 years in their study (Table 4).

In the present study, late cardiac and lung toxicities were minimal. RNI hardly contributes to the dose to the heart so there may not be any concern of late toxicity to this organ from RNI. Late cardiac toxicity in the present study even with RNI is comparable to the START data. Although more than half of our patients (56.5%) had received anthracycline based chemotherapy, there was no excess cardiac toxicity. Hypofractionation studies from Belgium [14] and Thailand [15] on RNI and have not reported excess late cardiac toxicity. In our series of internal mammary node irradiation with hypofractionation with a median follow-up of 14 years there was

**Table 2.** Late toxicities (n = 1,770)

| Late toxicity | Number of patients (%) | 95% CI | Prevalence | | |
|---|---|---|---|---|---|
| | | | At 5 years | At 10 years | At 15 years |
| Arm/shoulder pain (moderate/marked) | 254 (14.3) | 12.7–16.1 | 141/1,254 (11.3) | 74/856 (8.6) | 37/418 (9.2) |
| Shoulder stiffness (moderate/marked) | 219 (12.3) | 10.9–14.0 | 111/1,254 (8.8) | 61/856 (7) | 27/415 (6.5) |
| Arm edema (moderate/marked) | 131 (7.4) | 6.2–8.7 | 95/1,353 (7.0) | 62/854 (7.2) | 30/420 (7.1) |
| Cardiac (grade 3) | 29 (1.6) | 1.1–2.3 | 9/1,242 (0.7) | 13/831 (1.5) | 7/415 (1.6) |
| Lung (grade 3) | 23 (1.3) | 0.8–1.9 | 9/1,231 (0.7) | 9/827 (1) | 5/412 (1.2) |
| Rib fracture | 6 (0.3) | 0.1–0.7 | 2/1,254 (0.1) | 2/854 (0.2) | 2/418 (0.5) |
| Second malignancy | 105 (5.9) | 4.9–7.1 | 19/1,245 (1.5) | 39/837 (4.6) | 42/420 (10) |

Values are presented as number (%).

**Table 3.** Relationship between number of dissected nodes and arm edema (n = 1,770)

| | Number of patients | Arm edema | 95% CI | p-value for trend |
|---|---|---|---|---|
| Number of dissected nodes | | | | < 0.001 |
| ≤ 10 | 843 | 41 (4.9) | 3.5–6.5 | |
| 11–20 | 752 | 68 (9.0) | 7.1–11.3 | |
| > 20 | 175 | 22 (12.6) | 8.0–18.4 | |

Values are presented as number (%).
CI, confidence interval.


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no excess cardiac toxicity [9].

RNI does contribute dose to the lungs and may increase pulmonary toxicity but hypofractionated RNI has not been shown to increase its incidence as compared to standard fractionation [6]. With this dose fractionation pulmonary fibrosis rate was 1.3%. This is consistent to the less than 2% in the published studies [2,3,6]. There was no grade 3 late pulmonary toxicity in the study by Wang et al. [6], but they reported grade 1–2 toxicity rate of 15% (Table 4). This is also comparable to the EORTC study (1.3%–4.3%) [16]. Other studies on hypofractionated PMRT and RNI with limited patient numbers have also demonstrated reduced risk of pulmonary toxicity as compared to the standard fractionation [14,15,17]. In a study from Greece, intense asymptomatic radiographic findings of infield lung fibrosis were noted in 4 of 112 (3.6%) patients with amifostine protection [17]. We could not find any association between the dosimetric factors and lung and heart toxicities in these patients, this may be because of dosimetry was done in small number of patients.

The rates of moderate/marked lymphedema of 7.4% in our study are also within the range reported in the literature (Table 4). Lateral border of supraclavicular field in the present study was deltoid insertion which means brachial plexus and shoulder joint were within the radiation field in these patients (Fig. 1B). Since this reported rate is with 2D technique, it would be likely less with modern 3D technique where deltoid and pectoral muscles, lateral SCF and shoulder joint are no more part of the RNI target volume. RNI field size following the ESTRO and RTOG guidelines are smaller than the conventional 2D fields thus sparing more normal tissue [18,19]. Our lymphedema rates are also comparable to the AMAROS study where it was 11% at 5 years [20]. RNI has been shown to increase arm lymphedema from 5%–10% after whole-breast irradiation (WBI) to 10%–60% with PMRT [20-27]. A Canadian study reported that lymphedema rate increased from 4.1% to 7.3% after WBI only [26]. In our study lymphedema rate significantly increased with the number of axillary lymph nodes dissected (Table 3). In START trials lymphedema rate ranged from 3.7% to 16.8% with hypofractionation as compared to 7.8% to 12.8% with conventional fractionation [4]. In the START trials, there were only 51–80 and 20–36 patients per arm at 5 and 10 years and number of events ranged from 0–5 and 0–2 at 5 and 10 years, respectively. Khan et al. [8] reported lymphedema in 4.5% patients at a median follow-up of 32 months. Wang et al. [6] reported grade 1–2 and grade 3 lymphedema rate of 20% and 1%, respectively, in the hypofractionation arm. A study from Thailand also did not report any excess increase in the radiation-induced lymphedema as compared to conventional fractionation [15].

So far, we have not seen any brachial plexopathy with this dose fractionation. With conventional RT regimen the incidence of brachial plexopathy has been reported to be less than 5% and paraesthesia up to 20% [27]. If we consider $\alpha/\beta$ of 2 for brachial plexus, the BED delivered with this regimen would be 93 Gy compared to 100 Gy with standard fractionation. The dose fractionation schedule in the present study does not exceed tolerance of critical structures in the SCF and axilla. So there are likely less chances of de-

**Table 4.** Late toxicities with hypofractionation studies in breast cancer

| Study | Year | Number of participants | Population | Dose (Gy) | Fractions | Pulmonary | Cardiac | Arm edema | Shoulder dysfunction |
|---|---|---|---|---|---|---|---|---|---|
| START A trial [4] | 2013 | 2,236 | Low risk | 39 | 13 | 1.2% | 1.5% | 6.5% | 10.5% |
| | | 14% RNI | | 41.6 | 13 | 1.1% | 1.1% | 16.8% | 8.7% |
| START B trial [4] | 2013 | 2,215 | Low risk | 40 | 15 | 1.7% | 1.5% | 3.7% | 3.7% |
| | | 7% RNI | | | | | | | |
| Whelan et al. [7] | 2010 | 1,234 | Low risk | 42.56 | 16 | NR | NR | 4.1%–7.3% | NR |
| Wang et al. [6] | 2019 | 820 | High risk | 43.5 | 15 | G1-2: 15% | G3: 1% | G1-2: 19% | 3% |
| | | | | | | G3: 0% | | | |
| Pinitpatcharalert et al. [15] | 2011 | 215 | High risk | 42.4–47.7 | 16–18 | All toxicities were similar to conventional fractionation group | | | |
| Koukourakis et al. [17] | 2013 | 112 | High risk | 35 | 10 | 4% CT changes in lung | NR | G1-2: 11.6% | 1.8% |
| | | 65% RNI | | | | | | | |
| Van Parijs et al. [14] | 2012 | 70 | Low risk | 42 | 15 | ↓DLco 7% | 4.6% | NR | NR |
| | | 33% RNI | | | | | | | |
| Yarnold et al. [26] | 2005 | 1,410 | Low risk | 39 | 13 | NR | NR | 8.3% | 18.1% |
| | | 20% RNI | | 42.9 | | | | 5.9% | 7.1% |
| Present study | 2020 | 1,770 | High risk | 35/40 | 15 | 1.6% | 1.6% | 7.4% | 12.3% |

RNI, regional nodal irradiation; G, grade; NR, not reported; DLco, lung diffusion of carbon monoxide.

veloping brachial plexopathy with this dose schedule. There was no brachial plexopathy in the study by Wang et al. [6]. In the START trials brachial plexopathy was reported in only one patient in START A trial [1]. However, there was no adverse effect on shoulder or arm function in START B trial [2]. Our RNI regimen is similar to START B regimen (40 Gy/15 fx/3 weeks) which is equivalent to 47 Gy in 2.0-Gy fractions if the $\alpha/\beta$ value for brachial plexus is 2.0 Gy or to 49 Gy in 2.0-Gy fractions, if $\alpha/\beta = 1.0$ Gy [28]. There are no data from a Royal Marsden study on RNI [29]. In a study from Greece where they treated 73/112 patients (65%) with RNI, none had brachial plexopathy [17]. About 21% of patients in the present study received taxanes. Still, we did not observe an increase in arm paraesthesia and brachial plexopathy with this RT schedule. In our past series of PMRT and RNI also we have not observed excess risk of arm edema or brachial plexopathy [8-12].

Of all second malignancies majority 61 (58%) were in the opposite breast. Out of 44 non-breast second malignancies 6 (5.7%) were associated with RT. Breast and non-breast second malignancy risk associations have been discussed in detail and published previously from our department [30-32].

World's 85% population lives in low-middle income countries [33]. As breast cancer is a leading cancer in females and RT is an important part of its locoregional management, hypofractionation will reduce the waiting time for radiation in the limited resource countries. Hypofractionation also reduces treatment time to half with similar control rates and lesser late toxicities compared to conventional fractionation with economic gain. In low-in-come countries with limited resources where 3D treatment is not possible, 2D treatment with modification of the RT fields as per ESTRO and RTOG guidelines may be possible.

Limitations of the study are its retrospective nature, single institutional and inclusion of limited patients who received IMNI. The minimal cardiac toxicity of this study should be interpreted with caution in this context. Although all the patients were treated with simple 2D RT technique but dose delivered was similar to standard hypofractionation which is likely to be future of PMRT and RNI. Since majority of patients with breast cancer in the developed world at present are treated with modern techniques like 3D conformal RT or intensity-modulated RT, likely risk of late toxicities in these patients would be less. The current study may not reflect the late toxicity that we have with current RT techniques. But in the limited resource countries majority of breast cancer patients are still treated with 2D technique as it is simple to plan and execute. Field sizes used always depend on the anthropometry of the patient, so it is also an individualised treatment. For breast cancer postoperative RT, 2D or 3D techniques may not make a difference if the dose used is within this hypofractionation schedule with proper planning and field alignment. Postoperative pre-RT toxicity is not reported here. Patient reported outcomes will be part of a separate study. Very few patients in the study received trastuzumab because of economic reasons so its impact on outcomes and late cardiac toxicity cannot be evaluated. None of our patients had undergone breast reconstruction so it would be difficult to comment on rates of complications in these patients. Last two situations are common in the limited resource countries.

Strengths of the study are large numbers of patients with long-term, regular follow-up; patients with stage II and III breast cancer treated with hypofractionated RT to the chest wall and RNI including IMNI with same dose fractionation in all the patients, young as well as elderly patients with simple conventional 2D planning which is possible in any centre in any limited resource country with economic implications. The study may also add to the experience of hypofractionated RT with systemic treatment with anthracyclines and taxanes which raises concern of cardiac and pulmonary toxicity, paraesthesia, brachial plexopathy and lymphedema, respectively. From our experience, hypofractionated RT with anthracyclines and taxanes seems to be safe. The American Society for Radiation Oncology (ASTRO) has also realised that hypofractionation may be more acceptable to patients because of its convenience and economic benefit. They suggested that in women aged $\geq$50 years with early breast cancer, WBI should not be started without giving option of hypofractionation [34]. Recently ASTRO widened these recommendations to any age and stage [35]. However, such advisory for PMRT and RNI with shorter fractionations are lacking. Although retrospective, reporting these outcomes may strengthen data on hypofractionated PMRT and RNI. It may also encourage utilization of RT in limited resource countries where breast cancer patients travel long distance for treatment. It has its economic implications for the patient, family and for the country as a whole.

In conclusion, in women with breast cancer, after mastectomy 40 Gy/15 fx/3 weeks hypofractionated RNI with 2D technique seems to be safe and comparable to historical data of conventional fractionation.

## Conflict of Interest

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

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# Short-course versus long-course neoadjuvant chemoradiotherapy in patients with rectal cancer: preliminary results of a randomized controlled trial

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**Purpose:** Colorectal cancer is becoming an increasing concern in the middle-aged population of Iran. This study aimed to compare the preliminary results of short-course and long-course neoadjuvant chemoradiotherapy treatment for rectal cancer patients.

**Materials and Methods:** In this clinical trial we recruited patients with rectal adenocarcinoma located from 5 cm to 15 cm above the anal verge. Patients in group I (short-course) received three-dimensional conformational radiotherapy with a dose of 25 Gy/5 fractions in 1 week plus concurrent XELOX regimen (capecitabine 625 mg/m$^2$ from day 1–5 twice daily and oxaliplatin 50 mg/m$^2$ on day 1 once daily). Patients in group II (long-course) received a total dose of 50–50.4 Gy/25–28 fractions for 5 to 5.5 weeks plus capecitabine 825 mg/m$^2$ twice daily. Both groups underwent consolidation chemotherapy followed by delayed surgery at least 8 weeks after radiotherapy completion. The pathological response was assessed with tumor regression grade.

**Results:** In this preliminary report on complications and pathological response, 66 patients were randomized into two study groups. Mean duration of radiotherapy in the group II (long-course) was 5 ± 1 days (range, 5 to 8 days) and 38 ± 6 days (range, 30 to 58 days). The median follow-up was 18 months. Pathological complete response was achieved in 32.3% and 23.1% of patients in the short-course and long-course groups, respectively (p = 0.558). Overall, acute grade 3 or higher treatment-related toxicities occurred in 24.2% and 22.2% of patients in group I and II, respectively (p = 0.551). No acute grade 4 or 5 adverse events were observed in either group except one grade 4 hematologic toxicity that was seen in group II. Within one month of surgery, no significant difference was seen regarding grade ≥3 postoperative complications (p = 0.333).

**Conclusion:** For patients with rectal cancer located at least 5 cm above the anal verge, short-course radiotherapy with concurrent and consolidation chemotherapy and delayed surgery is not different in terms of acute toxicity, postoperative morbidity, complete resection, and pathological response compared to long-course chemoradiotherapy.

**Keywords:** Chemoradiotherapy, Clinical trial, Consolidation chemotherapy, Rectal Neoplasms, Dose hypofractionation, Iran

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## Introduction

Colorectal cancer is the third most common cancer in males and the fourth most common among females in Iran [1]. The incidence of rectal cancer in our country is relatively lower than that of Western countries; however, it has been increasing rapidly in recent years. According to a study by Malekzadeh et al. [2], the incidence of colorectal cancer has increased by 80% in the last 30 years in Iran. Interestingly, up to the age of 45 years, the incidence of this cancer in the Iranian population does not significantly differ compared with the US population. Therefore, colorectal cancer is becoming a serious problem for the young Iranian population and the workforce [3].

Currently, the routine treatment plan for locally advanced rectal cancers comprises of preoperative radiation with or without chemotherapy followed by surgery. To date, two types of neoadjuvant therapy have been introduced for rectal cancer. The first method, known as long-course chemoradiotherapy (LCRT) or conventional chemoradiotherapy, includes 45–54 Gy in 25–28 fractions along with concomitant chemotherapy—mainly 5-fluorouracil (5FU) or its derivatives—followed by delayed surgery 6–8 weeks later. This method is mostly applied in the United States and several European countries [4]. Another method is the Northern-European method (especially in Scandinavia and Poland), known as short-course radiotherapy (SCRT), which consists of 25 Gy in 5 fractions without concomitant chemotherapy followed by immediate surgery within 1 week after radiotherapy completion [5].

One of the disadvantages of conventional LCRT with concomitant chemotherapy is the prolongation of the treatment course and the interval between diagnosis and surgery. Moreover, LCRT is costly. Likewise, in our non-private center, patients experience long waiting times for LCRT, whereas the time spent for SCRT is one-fifth of that in LCRT.

In most studies, SCRT without chemotherapy has shown lower pathological response rates compared with conventional LCRT [6], and the addition of chemotherapy to SCRT has always been associated with a concern about increased complications [7]. In addition, no theoretical consensus currently exists on a SCRT regimen that will yield the highest response rate [8,9].

According to our previous studies on short-course and long-course treatment in rectal cancer patients, and the promising results achieved with SCRT, we aimed to compare these two methods in terms of safety profile, pathologic response, and survival in a randomized controlled trial [10,11]. Here, we report the preliminary results of this study by 50% of the expected accrual, including treatment complications and pathological complete response (pCR). In the future, we will report late toxicities and survival rates.

## Materials and Methods

This study was a randomized controlled clinical trial conducted at the radiation oncology ward of Cancer Institute of Iran. Patient recruitment began in April 2016. Patients with a confirmed histological diagnosis of rectal adenocarcinoma located within 5 to 15 cm from the anal verge, and cT3-4 stage or node positive status—based on magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS)—were enrolled in the study. We excluded patients with distant metastasis, an Eastern Cooperative Oncology Group performance score >1, non-operable status or intolerance to chemotherapy, a history of current or past second malignancy, recurrence after previous surgery, and cases of familial adenomatous polyposis (FAP).

The pre-treatment evaluation consisted of imaging modalities such as pelvic MRI, EUS, and thoracoabdominal computed tomography (CT) scan and lab tests including complete blood count, liver and renal function tests, and serum carcinoembryonic antigen (CEA). After completion of staging workup examinations, patients who met the eligibility criteria were given informed consents. Patients who were willing to take part in the study were then randomly assigned either to the short-course or long-course treatment group. Patients of each group were matched in terms of stage of cancer. Randomization was based on permuted block method. Due to the nature of the study intervention, blinding of participants to the assignment group was not possible. In order to minimize patient loss and withdrawal, the investigators followed participants by telephone. After initiation of the study, physical examination and lab tests were performed weekly to assess post-treatment complications. The treatment regimen of group I (short-course) consisted of three-dimensional conformational radiotherapy (3D-CRT) with a total dose of 25 Gy in 5 fractions in 1 week plus concurrent XELOX (capecitabine 625 mg/m$^2$ twice daily from day 1 to 5 and oxaliplatin 50 mg/m$^2$ intravenous injection day 1 only). As for group II (long-course), patients underwent 3D-CRT with a total dose of 50–50.4 Gy in 25–28 fractions during 5 to 5.5 weeks plus concurrent capecitabine 825 mg/m$^2$ twice daily. Capecitabine tablets were provided by the Actero Middle East Company (a.k.a. Actero Pharma in Tehran, Iran) for all participants. Patients of both groups underwent delayed surgery 8 weeks after the completion of radiotherapy which was performed in either the surgical oncology ward or the colorectal surgery ward. They also received pre-operation chemotherapy with XELOX 3 to 4 weeks after radiotherapy completion.

### 1. Outcome assessment

The primary outcome of interest was acute toxicity during chemo-


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radiotherapy up to 1 month of its completion based on the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. In the present report, the secondary outcomes were pCR and down-staging, complete resection, and post-operative morbidity. Pathological response was defined by tumor regression grade (TRG). We used the modified Ryan system that had been endorsed by the American Joint Committee on Cancer [12]. Overall down-staging was defined as conversion of clinical stage to ypT0-2N0, which is considered as non-locally advanced disease. Tumor down-staging was defined as the conversion of primary tumor to ypT0-2. Nodal down-staging was characterized only among those with cN1-2 if ypN was less advanced than cN. Post-operative morbidity was characterized as any toxicity attributable to surgery up to 1 month after the procedure.

### 2. Treatment planning

Contouring of clinical target volume (CTV) was based on the Radiation Therapy Oncology Group consensus [13]. Delineation of lymph node basins at risk was based on the international guideline by Valentini et al. [14]. Planning target volume (PTV) was generated by planning software and with adding an 8-mm margin in all dimensions. Before initiation of treatment, the definite treatment plan was approved by the patients' physician regarding 95% dose coverage of PTV, dose and location of $D_{max}$, and dose to organs-at-risk.

### 3. Statistical analysis

Sample size was calculated according to a previous study performed at this center and another study in which the reported incidence of grade ≥2 toxicity was 50% and 75% in SCRT and LCRT, respectively [10,15]. The power was 80% and type I error (α) was 0.05. Taking into account a 10% loss, the required sample size was calculated as 120 patients (60 in each group).

Since this was a preliminary analysis, we included 50% of the total expected accrual size. We used the following formula to calculate sample size [16]:

$$n = (Z_{\alpha/2} + Z_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2)) / (p_1-p_2)^2$$

For evaluating pCR and surgical and chemoradiotherapy complications, the chi-square test and multivariate logistic regression were used. A p-value of less than 0.05 was considered as statistically significant.

### 4. Ethical considerations

Informed consent was obtained from all participants prior to enrollment in the study. This study was approved by the Ethics Committee of Tehran University of Medical Sciences and the Iranian Registry of Clinical Trials (Ethics Code: IR.TUMS.VCR.REC.1396.3475, IRCTID: IRCT2017110424266N3).

## Results

Initially, 123 patients were recruited; however, after consideration of inclusion and exclusion criteria, only 66 patients were allocated to receive either SCRT (group I) or LCRT (group II). No patient was lost to follow-up or discontinued intervention (Fig. 1).

### 1. Baseline characteristics

The baseline characteristics of patients in both groups are demonstrated in Table 1. As shown, there was no significant difference between the two groups in respect to the studied variables. The median age of patients in the short-course and long-course treatment groups was 56 ± 10.3 and 53 ± 12.9 years old, respectively. In both groups, the majority of patients had a histologic grade 1 tumor.

### 2. Acute treatment toxicity

The mean duration of radiotherapy course in the SCRT and LCRT groups was 5 ± 1 and 38 ± 6 days, respectively. Grade 2 and higher acute adverse events (AEs) were observed in 75.8% and 61.5% of patients in group I and II, respectively (p = 0.19). The percentage for grade 3 and higher AEs in the concurrent chemoradiotherapy period was 15.2% and 14.8%, respectively (p = 0.63). No grade 4 or 5 radiotherapy-induced adverse event was observed except one grade 4 hematologic toxicity in the LCRT group.

Grade 3 and higher AEs related to preoperative chemotherapy (consolidation) were observed in 12.1% and 11.5% of patients in group I and II, respectively (p = 0.64). Preoperative chemotherapy tolerance (receiving full planned dose) in group I and II was 87.9% and 81.8%, respectively (p = 0.4). Collectively, grade 3 or higher acute treatment toxicities acute treatment toxicities, including chemoradiotherapy- and consolidation chemotherapy-attributable AEs, were seen in 24.2% and 22.2% of patients in group I and II, respectively (p = 0.55).

The frequency of the most severe acute toxicities is demonstrated in each treatment group (Table 2).

### 3. Surgical outcomes

Fifty-five percent of the surgical specimens were re-examined by a skilled pathologist. TRG was altered in 6/33 (18.2%) cases; of note, however, only one change from grade 1 to grade 0 was observed, and the majority of changes were between grades 2 and 3. A pCR (final TRG = 0) in the SCRT and LCRT groups was achieved in 32.2% and 23.1% of cases, respectively (p = 0.56); whereas a

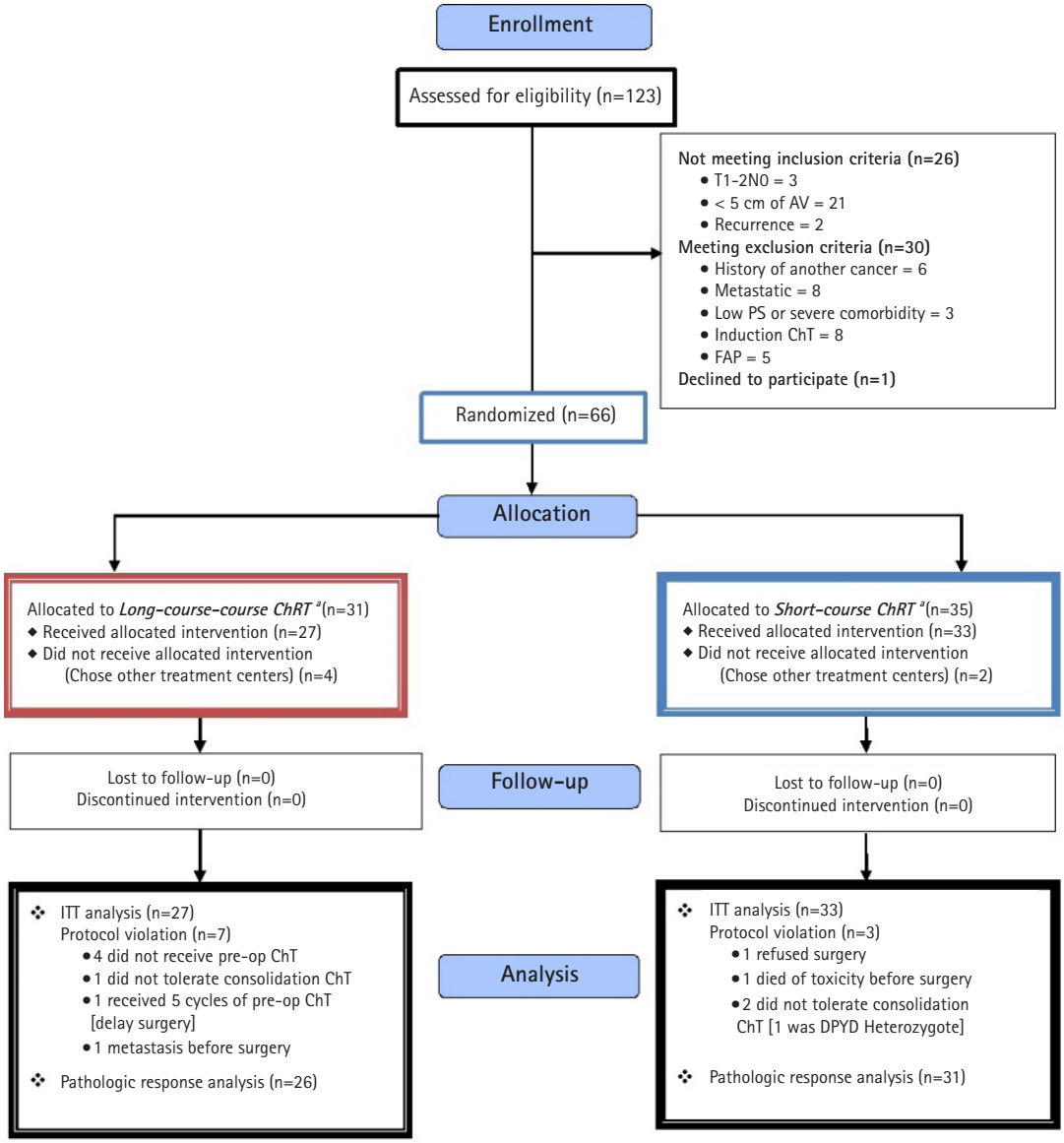


**Fig. 1.** CONSORT flow diagram of the study. AV, anal verge; PS, performance score; ChT, chemoradiotherapy; FAP, familial adenomatous polyposis; ITT, intention-to-treat.

pathological complete or near complete response (final TRG = 0–1) was seen in 41.9% and 42.3% of cases, respectively (p = 0.99). One patient had ypT0N1 that was considered TRG = 0, however, his/her surgical stage was classified as stage 2. Tumor down-staging (ypT0-2 ypN0, based on the definition) occurred in 54.8% and 53.8% of the cases in group I and II, respectively (p = 0.58). Detailed data is shown in Table 3.

## 4. Post-operative morbidity

The frequency of grade 3 or higher post-operative morbidities (within 1 month after surgery) in the SCRT and LCRT groups was 19.4% and 11%, respectively (p = 0.33). No post-operative mortality was observed. The type of post-operative morbidities in each group is shown in Table 4.

## 5. Late treatment toxicity

The frequency of grade 2 or higher late treatment toxicities (at least 6 months after radiotherapy) in the SCRT and LCRT groups were 38.7% and 38.4%, respectively (p = 0.56); while grade 3 and higher toxicities were seen in 6.5% and 11.5% of the patients in group I and II, respectively (p = 0.16) (Table 5). The frequency of late treatment toxicities varied based on the ward in which surgeries were performed (Table 6); in the colorectal surgery ward, toxicities were less frequently observed in patients who received the

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**Table 1.** Baseline characteristics of patients in both treatment groups

| | Short-course | Long-course | p-value |
|---|---|---|---|
| Age (yr) | 56 ± 10.3 (39–81) | 53 ± 12.9 (31–76) | 0.14 |
| Sex | | | 0.35 |
| Female | 15 | 10 | |
| Male | 18 | 17 | |
| Distance from anal verge (cm) | 9 ± 2.6 | 8 ± 3.0 | 0.80 |
| Pathology to RT (wk) (n = 53) | 6 ± 4.4 (3–23) | 6 ± 5.9 (2–34) | 0.21 |
| PTV ($cm^3$) | 1,048 ± 269 (850–1,823) | 1,115 ± 289 (844–2,049) | 0.51 |
| ECOG performance status | | | 0.44 |
| 0 | 14 | 10 | |
| 1 | 19 | 17 | |
| Diversion colostomy | 2 (6.1) | 2 (7.4) | 0.61 |
| Elevated CEA (n = 51) | 7 (29.2) | 12 (44.4) | 0.20 |
| Histological grade (n = 48) | | | 0.47 |
| 1 | 12 (48) | 11 (47.8) | |
| 2 | 11 (44) | 7 (30.4) | |
| 3 | 2 (8) | 4 (17.4) | |
| 4 | 0 (0) | 1 (4.3) | |
| Mucinous carcinoma (n = 52) | 2 (6.5) | 5 (23.8) | 0.08 |
| Clinical stage | | | 0.08 |
| II | 8 | 2 | |
| III | 25 | 25 | |
| Clinical T status (n = 60) | | | 0.048 |
| 2 | 0 | 4 (14.8) | |
| 3 | 30 (90.9) | 19 (70.4) | |
| 4 | 3 (9.1) | 4 (14.8) | |
| Clinical N status (n = 60) | | | 0.109 |
| 0 | 8 (24.2) | 2 (7.4) | |
| 1 | 18 (54.5) | 14 (51.9) | |
| 2 | 7 (21.2) | 11 (40.7) | |

Values are presented as median ± standard deviation (range) or number (%).
RT, radiotherapy; PTV, planning tumor volume; CEA, carcinoembryonic antigen.

**Table 2.** Frequency of the most severe acute toxicities in SCRT (group I) and LCRT (group II) before consolidation chemotherapy

| Toxicity | Group | Highest grade of acute toxicity during concurrent chemoradiotherapy | | | |
|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 |
| Proctitis | I | 8 (24.2) | 18 (54.5) | 5 (15.2) | - |
| | II | 9 (33.3) | 8 (29.6) | 2 (7.4) | - |
| Diarrhea | I | - | 2 (6.1) | - | - |
| | II | - | 1 (3.7) | 2 (7.4) | - |
| Hematologic | I | - | - | - | - |
| | II | - | 2 (7.4) | - | 1 (3.7) |
| Urinary | I | - | - | - | - |
| | II | - | 1 (3.7) | - | - |

Values are presented as number (%).
SCRT, short-course chemoradiotherapy; LCRT, long-course chemoradiotherapy.

**Table 3.** Characteristics of surgeries and response to neoadjuvant treatment in the SCRT and LCRT groups

| | Short-course | Long-course | p-value |
|---|---|---|---|
| Interval between start of RT and surgery (wk) | 11 ± 3.9 (6-28) | 18 ± 6.6 (11-39) | <0.001 |
| Interval between end of RT and surgery (wk) | 10 ± 3.9 (6-28) | 12 ± 6.6 (6-34) | 0.004 |
| Surgery center (n = 52) | | | 0.19 |
| Surgical oncology ward | 19 (73.1) | 15 (57.7) | |
| Colorectal surgery ward | 7 (26.9) | 11 (42.3) | |
| Surgical technique | | | 0.33 |
| Open LAR or VLAR | 28 (90.3) | 23 (88.5) | |
| APR | 0 | 1 (3.8) | |
| Laparoscopic LAR | 1 (3.2) | 2 (7.7) | |
| Total proctocolectomy | 2 (6.5) | 0 (0) | |
| Sphincter preservation | 31 (100) | 25 (96.2) | 0.50 |
| Surgical stage | | | 0.99 |
| 0 | 9 (29) | 7 (26.9) | |
| I | 8 (25.8) | 7 (26.9) | |
| II | 10 (32.3) | 9 (34.6) | |
| III | 4 (12.9) | 3 (11.5) | |
| Surgical N stage (ypN) | | | 0.46 |
| 0 | 27 (87.1) | 23 (88.5) | |
| 1 | 4 (12.9) | 2 (7.7) | |
| 2 | 0 (0) | 1 (3.8) | |
| Resected nodes | 8 ± 6.1 (0-23) | 9 ± 9.1 (0-39) | 0.55 |
| Positive lymph node ratio | 0.02 ± 0.06 (0-0.25) | 0.04 ± 0.15 (0-0.71) | 0.47 |
| Surgical T stage (ypT) | | | 0.46 |
| 0 | 10 (32.3) | 7 (26.9) | |
| 1 | 2 (6.5) | 1 (3.8) | |
| 2 | 6 (19.4) | 6 (23.1) | |
| 3 | 10 (32.3) | 12 (46.2) | |
| 4a | 3 (9.7) | 0 (0) | |
| Residual tumor size (cm) (n = 25) | 2.5±2.48 (1-11) | 2.3±0.9 (1-4.5) | 0.27 |
| R0 resection (No +ve/close margin ) | 31 (100) | 25 (96.2) | 0.46 |
| Tumor regression grade | | | 0.29 |
| 0 | 10 (32.3) | 6 (23.1) | |
| 1 | 3 (9.7) | 5 (19.2) | |
| 2 | 16 (51.6) | 10 (38.5) | |
| 3 | 2 (6.5) | 5 (19.2) | |
| Perineural invasion (n = 52) | 4 (14.3) | 2 (8.3) | 0.41 |
| Lymphovascular invasion (n = 52) | 4 (14.3) | 8 (33.3) | 0.10 |
| Down staging | 25 (80.6) | 22 (84.6) | 0.49 |
| Tumor down staging (ypT0-2) | 18 (58.1) | 14 (53.8) | 0.48 |
| Nodal down staging (ypN0) | 27 (87.1) | 23 (88.5) | 0.60 |

Values are presented as median ± standard deviation (range) or number (%).
SCRT, short-course chemoradiotherapy; LCRT, long-course chemoradiotherapy; LAR, low anterior resection; VLAR, very low anterior resection; APR, abdominal perineal resection.

**Table 4.** Frequency and type of postoperative morbidities in SCRT and LCRT groups

| Type of postoperative modalities | Short-course | Long-course |
|---|---|---|
| None | 25 (75.8) | 23 (85.2) |
| Wound complication | 3 (9.1) | 2 (7.4) |
| Ostomy failure | 1 (3.0) | - |
| Abscess (presacral) | 2 (6.1) | 1 (3.7) |

Values are presented as number (%).
SCRT, short-course chemoradiotherapy; LCRT, long-course chemoradiotherapy.


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**Table 5.** Late treatment toxicities and frequency of the most severe complications in SCRT (group I) and LCRT (group II)

| Toxicity | Group | Highest grade of late toxicity | | |
|---|---|---|---|---|
| | | 1 | 2 | 3 |
| Proctitis | I | 13 (39.4) | 9 (27.3) | - |
| | II | 9 (33.3) | 4 (14.8) | 1 (3.7) |
| Fistula | I | - | - | 1 (3.0) |
| | II | - | 1 (3.7) | - |
| Renal failure | I | - | - | - |
| | II | - | 1 (3.7) | - |
| Fibrosis/stenosis | I | - | - | 1 (3.0) |
| | II | - | - | 1 (3.7) |
| Small bowel obstruction | I | - | 1 (3.0) | - |
| | II | - | 1 (3.7) | - |
| Dermatitis | I | - | - | - |
| | II | - | - | 1 |

Values are presented as number (%).
SCRT, short-course chemoradiotherapy; LCRT, long-course chemoradiotherapy.

short-course treatment compared with patients who received long-course treatment (p = 0.02).

## Discussion and Conclusion

We evaluated the preliminary outcomes of SCRT with concomitant XELOX regimen in comparison to LCRT with concomitant capecitabine. Both study groups received consolidation chemotherapy with XELOX at the resting interval before surgery. The reason for administering XELOX in the concurrent regimen of patients undergoing SCRT was the promising results we achieved in the previous single-arm study conducted at our institution [10]. Also, another study published a few years ago showed that the addition of oxaliplatin leads to more robust down-staging compared with capecitabine alone [17]. Considering these results, we aimed to investigate the efficacy and safety of XELOX regimen for concurrent chemotherapy in SCRT as a potential alternative option compared with the standard treatment, which is LCRT with fluorouracil or capecitabine. As for the consolidation regimen, we used the adjuvant therapy for locally advanced rectal cancer, which is primarily XELOX, since oxaliplatin has been reported to enhance disease-free survival compared with capecitabine alone or fluorouracil plus leucovorin alone [18,19].

Some patients experienced a relatively long interval from radiation completion to surgery. These outliers were either due to temporary loss to follow-up, long waiting lists of the surgical wards, or occasional lack of coordination between the departments. Although none of the patients experienced re-growth of the tumor at the time of surgery, this issue should be taken into consideration since interval prolongation might affect pathological response.

**Table 6.** Comparison of late treatment toxicities (grade 3 or higher) between colorectal surgery ward and surgical oncology ward

| | Short-course | Long-course | Total | p-value |
|---|---|---|---|---|
| Colorectal surgery ward | 0 (0) | 2 (15.4) | 2 (6.5) | 0.02 |
| Surgical oncology ward | 2 (28.6) | 0 (0) | 2 (11.1) | 0.14 |
| p-value | 0.35 | 0.53 | 0.68 | |

Values are presented as number (%).

In this study, there was no significant difference in respect to acute treatment toxicities and post-operative morbidities between the short-course and long-course treatment groups. In LCRT, the peak of radiotherapy adverse events, including proctitis, enteritis, diarrhea, and mucositis is within the third to fifth week of treatment and the severity of the acute toxicities will gradually decrease 3 to 4 weeks after the completion of therapy. In this group, the patient receives chemotherapy simultaneously along with radiotherapy at the time when toxicities are at their peak, which can affect the severity of toxicities [20]. It is assumed that more acute toxicities are faced in the short-course treatment which uses the hypofractionated regimen, as it is a kind of accelerated regimen. According to a previous Polish study, in SCRT, acute toxicities peak at the 11th to 14th day after radiotherapy. At this time, the patient is resting after a 5-day treatment course, so he/she is not exposed to chemotherapy or radiotherapy; on the other hand, delaying the surgery for at least 8 weeks after irradiation will reduce the severity of toxicities [21]. In SCRT, malignancy symptoms (obstruction, bleeding, rectal discomfort) resolve sooner due to larger fractions and thus, influence the decline in the feeling of discomfort from acute toxicities. The lack of statistically significant difference in acute toxicities between the two groups can be explained by the mentioned reasons.

Another interesting finding of this study was that despite a smaller equieffective dose of radiotherapy (EQD2 = 31.25 Gy vs. 50 Gy) and also a smaller total chemotherapy dose (5 days vs. 25 days of capecitabine delivery) in the SCRT group, short-term oncologic outcomes were the same in both groups. More interestingly, in the SCRT group, the pCR was higher than that in most of the previous similar studies [22-27]. This finding can be rationalized by the fact that the large fractions used in a hypofractionated radiotherapy regimen can induce an immune response that will eventually increase the biologic effects of concomitant and consolidation chemotherapy. This immune response results from the release of a great number of antigens due to the breakdown of tumoral cells, and the presentation of these antigens to T cells [28,29]. Nevertheless, this hypothesis needs further assessment.

**Table 7.** Comparison of previous similarly designed studies with this study

| Study | Year | Number of participants | Design | Target interval from radiation end to surgery (wk) | Response | Toxicity |
|---|---|---|---|---|---|---|
| Sauer et al. [33] | 2004 | 823 | Neo-RT 50.4/28 + 5FU (1st & 5th wk) vs. Adj-RT 50.4/28 + 5FU (1st & 5th wk) | 6 | (Neo) pCR = 8%<br>(Neo) R0 = 91% | (Neo) Acute G3/4 = 27%<br>(Neo) Late G3/4 = 14% |
| Ngan et al. [27] | 2012 (TROG 01.04) | 326 (T3N0-1) | Neo-RT 25/5 immediate Sx vs. Neo-RT 50.4/28 + Infusional 5FU all days | Immediate vs. 4–6 | (LCRT) pCR = 15%<br>(LCRT) R0 = 96%<br>(SCRT) pCR = 1% | (LCRT) Late G3/4 = 8.2% |
| Yeo et al. [22] | 2013 (KROG 10-01) | 73 | Tomotherapy 25/5 + Bolus 5FU + LV d1-5 | 4–8 | ypT0-2N0 = 28.2%<br>pCR = 1.4% | G3/4 = 3.8% |
| Myerson et al. [26] | 2014 | 76 | IMRT 25 Gy/5 fx Then 4*mFOLFOX6 | 13–18 | pCR = 25% | Acute (preoperative) G3/4 non-hematologic = 21% |
| Beppu et al. [23] | 2015 | 20 | 4*S1 + Oxali ± Erbitux > RT 25/10/bid | 4 | pCR = 10% | G3/4 = 30% |
| Bujko et al. [24] | 2016 | 515 | RT 25/5 Then 3*FOLFOX4 vs. RT 50.4/28 + weekly Oxali + 5FU/LV (1st & 5th wk) | 6 | pCR = 16% vs. 12% | Acute G3/4 = 23% vs. 21%<br>Late = 20% vs. 22% |
| Chung et al. [25] | 2016 | 72 | RT 25/5 + 5FU d1-2 Then 3*5FU/LV vs. 50.4/28 + Bolus 5FU/LV (1st & 5th wk) | 6–8 | pCR = 21.1% vs. 13.2% | NS |
| Aghili et al. [10] | 2018 | 33 | RT 25/5 + Oxali 85/m2/d1 & Cap 825/m2/bid/d1-5 Then CapOx | 8–12 | pCR = 30.8%<br>R0 = 100% | Late G3 = 24.5% (up to 3-mo postop)<br>Acute RT G3 proctitis = 21.2% |
| Present study | - | 60 | RT 25/5 + Oxali 50/m2/d1 & Cap 625/m2/bid/d1-5 Then 1* CapOx vs. RT 50/25 + Cap 825/m2/bid Then 1*CapOx | 8–12 | pCR = 32.3% vs. 23.1%<br>R0 = 100% vs. 96.1% | Acute G3/4 = 24.2% vs. 22.2%<br>Late G3/4 = 6.5% vs. 11.5% |

RT, radiotherapy; SCRT, short-course chemoradiotherapy; LCRT, long-course chemoradiotherapy; 5FU, 5-fluorouracil; LV, leucovorin; pCR, pathologic complete response.

Comparison of our study with other similarly designed studies in which chemotherapy is applied along with SCRT concluded that we had reached more favorable outcomes (Table 7). So, the question is why short-course chemoradiation has produced such a good result. There are several reasons that could explain the more favorable results in this study; firstly, the precise delineation of target volumes based on international guidelines [14] and the strict confirmation of treatment plans, considering the sufficient coverage of PTV and also the dose of organs-at-risk; second, administration of capecitabine with radiotherapy instead of bolus 5FU is shown to be associated with fewer toxicities and higher response rates in a study by Haddad et al. [30]; third, prolonging the interval between radiotherapy completion and surgery to more than 8 weeks, as this has been demonstrated by Rega et al. [31] to reduce adverse events and increase response to neoadjuvant therapy. In our study, the interval from end of radiotherapy to surgery was higher compared with the majority of other similar studies. Consistent with our trial, a study by Myerson et al. [26], with a similar interval of 17 weeks, reported pathological responses comparable to our results; moreover, delivering consolidation chemotherapy before surgery which has been shown to be associated with an increase in complete response rates in a study by Habr-Gama et al. [32]; addition of oxaliplatin to capecitabine simultaneously with radiotherapy, which despite controversies, has been proved to increase response rates [17]; and lastly, performing operations in a more specialized ward for colorectal surgery by skilled and experienced colorectal surgeons.

In conclusion, SCRT versus LCRT with consolidation chemotherapy and delayed surgery were not significantly different in regards to acute toxicities, post-operative morbidities, complete resection, and pathological response. However, we should wait longer to be able to make a definitive comment on local recurrence, distant recurrence, survival rates, and late toxicities. Since our patients were only followed for a relatively short period of 18 months, results on these long-term measures will be reported separately in future studies. Prospective studies should focus on using novel radiotherapy techniques for reducing grade 2 acute and late AEs. Moreover, comparison of SCRT with sequential versus simultaneous chemo-


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therapy, investigation of tumor and mesorectum dose-escalation with SCRT to increase pCR rates, and implementation of a watch-and-wait approach after SCRT + chemotherapy is suggested. Conclusively, re-performing the current study with removal of simultaneous oxaliplatin, and based on the substantial pCR, and investigating sphincter preservation in lower rectal tumors (less than 5 cm from the anal verge) is recommended.

## Conflict of Interest

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

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# The predictive value of serum myeloma protein in solitary plasmacytoma

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**Purpose:** To identify the clinical usefulness of serum M protein and to establish a rationale for regular follow-up with serum protein electrophoresis in solitary plasmacytoma.

**Materials and Methods:** Sixty-nine patients with solitary plasmacytoma and solitary plasmacytoma with minimal marrow involvement according to the International Myeloma Working Group criteria were retrospectively reviewed.

**Results:** At a median follow-up of 6.2 years, 5-year local control (LC), 5-year multiple myeloma-free survival (MMFS), 5-year failure-free survival (FFS), and 5-year overall survival (OS) were 82.6%, 44.1%, 41.8%, and 85.1%, respectively. Among the patients whose initial serum M protein was present or not evaluated, 37.3% of patients showed disappearance of serum M protein after various treatment. MMFS of these patients were comparable to non-secretory plasmacytoma with undetectable levels of M protein, and significantly better than patients with persistent M protein. Increase of serum M protein ≥0.1 g/dL was most predictive of treatment failure with area under the curve of 0.731.

**Conclusion:** Patients who eventually showed persistence of serum M protein after treatment showed worse MMFS and FFS compared to those whose serum M protein disappeared or who had initially non-secretory disease. The increase of serum M protein level ≥0.1 g/dL from current nadir was predictive of treatment failure. Therefore, regular follow-up with serum M protein is highly recommended especially unless the patient had initially non-secretory disease.

**Keywords:** Plasmacytoma, Myeloma protein, Risk factor, Radiotherapy

## Introduction

Solitary plasmacytoma is a rare disease which accounts for less than 10% of plasma cell neoplasm [1]. It is diagnosed at a median age of 60 and is a male-dominant disease with a male to female ratio of approximately 2:1 [2,3]. Solitary plasmacytoma is subdivided into two disease entities. Solitary plasmacytoma originating from bones are classified as solitary plasmacytoma of the bone (SPB), whereas soft tissue origin plasmacytoma is classified as solitary extramedullary plasmacytoma (SEP). While SPB is most frequently observed in the axial skeleton, such as vertebra, SEP is commonly found in the head and neck, especially in the upper aerodigestive tract [2,3].

Owing to its rarity, there were no randomized trials to identify the standard treatment for solitary plasmacytoma. Although multiple myeloma (MM) is generally treated with chemotherapy and is thought to be incurable, solitary plasmacytoma is treated well with excellent 5-year local control (LC) rate ranging from 81 to 95% af-

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ter local radiation therapy (RT) [4–6]. Although there is no consensus regarding the optimal dose of RT, but RT dose ≥40 Gy was reported to improve LC [4,7]. Nevertheless, more than half of the patients after local or systemic treatment eventually progress to MM with long-term follow-up [3,4,8,9].

Although there is a consensus criteria for treatment response assessment for multiple myeloma [10], there is no widely used criteria for solitary plasmacytoma. Also, the prediction of treatment failure in solitary plasmacytoma patients is not available although early predictions of treatment failure is important considering the high rates of progressions to MM in order to make early salvage treatment possible.

Myeloma protein, which is also called M protein, is an abnormal protein produced in excess by an abnormal monoclonal proliferation of plasma cells and is typically detected in serum or urine of patients with MM or plasma cell tumors. Although only 3% of MM patients are non-secretory [11], i.e., no detectable serum and urine M protein at diagnosis, M protein is present in only 33% to 64% of solitary plasmacytoma patients at diagnosis [4,5,12,13]. Also in patients with M protein, the median level of serum M protein at diagnosis of solitary plasmacytoma patients is less than 1 g/dL [5,13], which is lower than that of MM (>3 g/dL) [11]. Nevertheless, the measurements of serum M protein level for solitary plasmacytoma is important in that the persistence of serum M protein after treatment was associated with poor prognosis [12–14] and therefore, the European Expert Panel recommended serum and urine electrophoresis and immunofixation to be performed during follow-up [15].

However, the usefulness of serum M protein as a biomarker to assess treatment response and to predict treatment failures in solitary plasmacytoma is yet to be studied. In MM, randomized trials implemented the increase in serum M protein more than 0.5 g/dL from nadir to define disease progression [16,17]. Considering the high incidence of non-secretory plasmacytoma and low level of serum M protein level at diagnosis, this criterion seems not to be appropriate for solitary plasmacytoma. Therefore, we tried to identify the clinical usefulness of serum M protein for predicting treatment failures and to establish a rationale for regular follow-up with serum protein electrophoresis to evaluate serum M protein level.

## Materials and Methods

### 1. Patients and diagnostic work-up

Medical records of patients with solitary plasmacytoma and solitary plasmacytoma with minimal marrow involvement according to the International Myeloma Working Group (IMWG) criteria [18] were retrospectively reviewed. A total of 69 solitary plasmacytoma patients who were taken care of between 1986 and 2019 at Seoul National University Hospital and Seoul National University Bundang Hospital were identified. At initial diagnostic work-up, all patients were evaluated with at least one radiological imaging work-ups (100.0%) including simple X-ray, CT, MRI, bone scan, or FDG-PET scan and laboratory work-ups including serum protein electrophoresis (62.3%), urine protein electrophoresis (55.1%), and serum free light chain ratio (31.9%).

The characteristics of all patients are shown in Table 1. The median age at the diagnosis of solitary plasmacytoma was 60.5 years (range, 29.7 to 79.8 years) and male was predominant (59.4%). The most common initial presenting symptom was pain at the involved site (59.4%). Vertebra was the most common primary site of the 51 SPB patients. Head and neck was the most common primary site of the 18 SEP patients. At initial diagnostic work-up, serum M protein, Bence Jones proteinuria, and abnormal free light chain ratio was present in 58.1%, 15.8%, and 50.0% of patients whose pre-treatment data was available, respectively. Patients treated with surgery alone or surgery plus adjuvant RT included more patients with insufficient initial work-up studies including serum and urine protein electrophoresis ($p < 0.05$) (Supplementary Table S1).

### 2. Treatment and follow-up

All patients received a curative treatment; definitive RT alone (46.4%), surgical resection (24.6%), and surgical resection plus adjuvant RT (17.4%). The median total radiation dose was 45.0 Gy (range, 23.4 to 70.0 Gy). Curative surgical resection was performed in 33 patients (47.8%) and 90.9% of them underwent complete resection. Chemotherapy was administered to 8 patients (11.6%). After the completion of treatment, patients were followed up with work-ups including radiological imaging studies, serum protein electrophoresis, and serum free light chain ratio. The median time from the initial serum protein electrophoresis at the time of diagnosis to first post-treatment serum protein electrophoresis was 3.5 months (range, 1.3 to 36.5 months). In this study, we defined the "disappearance of serum M protein" in order to assess treatment response. When post-treatment serum M protein of a patient whose initial serum M protein was present or not evaluated was measured and showed no detectable serum M protein during follow-up, it was regarded as disappearance of serum M protein.

Patients were defined as progression to MM, whenever meeting the criteria of IMWG for the diagnosis of MM during follow-up [18]. The diagnosis of MM requires clonal bone marrow plasma cells ≥10% or a biopsy-proven plasmacytoma plus the presence of one or more myeloma-defining events. Myeloma defining events include the presence of hypercalcemia, renal insufficiency, anemia, and bone lesion. Also, clonal bone marrow plasma cells ≥60%, se-


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**Table 1.** Patient characteristics of solitary plasmacytoma

| Characteristic | Number of patients (%) |
|---|---|
| Age (yr) | |
| < 60 | 32 (46.4) |
| ≥ 60 | 37 (53.6) |
| Sex | |
| Male | 41 (59.4) |
| Female | 28 (40.6) |
| Site of lesion | |
| SPB | 51 (73.9) |
| Craniofacial bone | 11 (15.9) |
| Vertebra | 21 (30.4) |
| Pelvic bone | 9 (23.1) |
| Extremity | 4 (5.8) |
| Others | 6 (8.7) |
| SEP | 18 (26.1) |
| Head and neck | 14 (20.3) |
| Others | 4 (5.8) |
| Anaplastic histology | |
| No | 67 (97.1) |
| Yes | 2 (2.9) |
| Serum M protein at diagnosis (g/dL) | |
| 0 | 18 (26.1) |
| 0.1–1.0 | 11 (15.9) |
| ≥ 1.1 | 14 (20.3) |
| Unknown | 26 (37.7) |
| Type of M protein | |
| IgG | 18 (72.0) |
| Light chain only | 2 (8.0) |
| Unknown | 5 (20.0) |
| Bence Jones proteinuria | |
| Absent | 32 (46.4) |
| Present | 6 (8.7) |
| Unknown | 31 (44.9) |
| Serum free light chain ratio | |
| Normal | 11 (15.9) |
| Abnormal | 11 (15.9) |
| Unknown | 47 (68.1) |
| Treatment | |
| RT only | 32 (46.4) |
| Surgery only | 17 (24.6) |
| Surgery + RT | 12 (17.4) |
| Chemotherapy alone | 3 (4.3) |
| RT + chemotherapy | 2 (2.9) |
| Surgery + chemotherapy | 1 (1.4) |
| Surgery + RT + chemotherapy[a] | 2 (2.9) |
| Radiation therapy[b] | |
| No radiation therapy | 22 (31.9) |
| < 45 GyEQD2 | 31 (44.9) |
| ≥ 45 GyEQD2 | 15 (21.7) |
| Surgical resection | |
| No surgical resection | 36 (52.2) |
| Partial resection | 3 (7.7) |
| Complete resection | 30 (43.5) |

SPB, solitary plasmacytoma of bone; SEP, solitary extramedullary plasmacytoma; RT, radiation therapy; EQD2, equivalent dose in 2-Gy fractions at $\alpha/\beta$ of 10.
[a]One patient received additional radiosurgery.
[b]One patient with unknown dose excluded.

rum free light chain ratio ≥ 100, or more than one focal lesion on MRI are diagnosed as MM regardless of the presence of myeloma defining event.

### 3. Statistical analysis

The characteristics according to various treatments were compared using Fisher's exact test. The actuarial LC, multiple myeloma-free survival (MMFS), failure-free survival (FFS), and overall survival (OS) were calculated with Kaplan-Meier analysis. All survivals were calculated from the first day of initial treatment. The events were local failure before progression to MM for LC, progression to MM or death from any cause for MMFS, any failure or death from any cause for FFS, and death from any cause for OS. Log-rank test was used for univariate analysis of the prognostic factors. Based on prognostic factors with $p < 0.05$, multivariate analysis was conducted. To identify a set of independent predictive factors a multivariate analysis with Cox proportional hazards model or Cox regression with Firth's penalized likelihood was performed as appropriate. In all analyses $p < 0.05$ was considered statistically significant. All statistical analyses were conducted in R version 3.5.0.

## Results

### 1. Survival outcome and cause of death

At a median follow-up of 6.8 years (range, 0.1 to 29.3 years), 9 patients (13.0%) experienced a local failure; 8 within 3 years and one at 9 years after treatment (Fig. 1A). The 5- and 10-year LC rate were 82.6% and 68.9%. The LC rates did not differ significantly across treatment modalities. Anaplastic plasmacytoma was the only prognostic factor for LC (Table 2, 3). In the meanwhile, RT improved LC for extramedullary lesions (100.0% vs. 53.6%; $p = 0.028$).

Overall, 32 patients (46.8%) progressed to MM. Most of the progressions to MM (96.9%) occurred within the first 5 years after treatment. The 5- and 10-year MMFS were 44.1% and 36.7%. In univariate analysis and multivariate analysis, SPB (hazard ratio [HR] = 8.63, $p = 0.036$), tumor size ≥ 5 cm (HR = 2.84, $p = 0.012$), and anaplastic histology (HR = 50.9, $p = 0.002$) were adverse prognostic factors for MMFS (Tables 2, 3). The 5- and 10-year FFS were 41.8% and 34.9%. As they were for MMFS, SPB (HR = 10.3, $p = 0.023$), tumor size ≥ 5 cm (HR = 2.18, $p = 0.043$), and anaplastic histology (HR = 66.6, $p = 0.001$) were significant adverse prognostic factors for FFS in the univariate and multivariate analysis (Tables 2, 3). The median OS was 14.0 years (95% confidence interval [CI], 11.8 years to upper limit not reached). The 5- and 10-year OS were 85.1% and 70.6%. There was no significant prognostic factor for OS (Table 4).

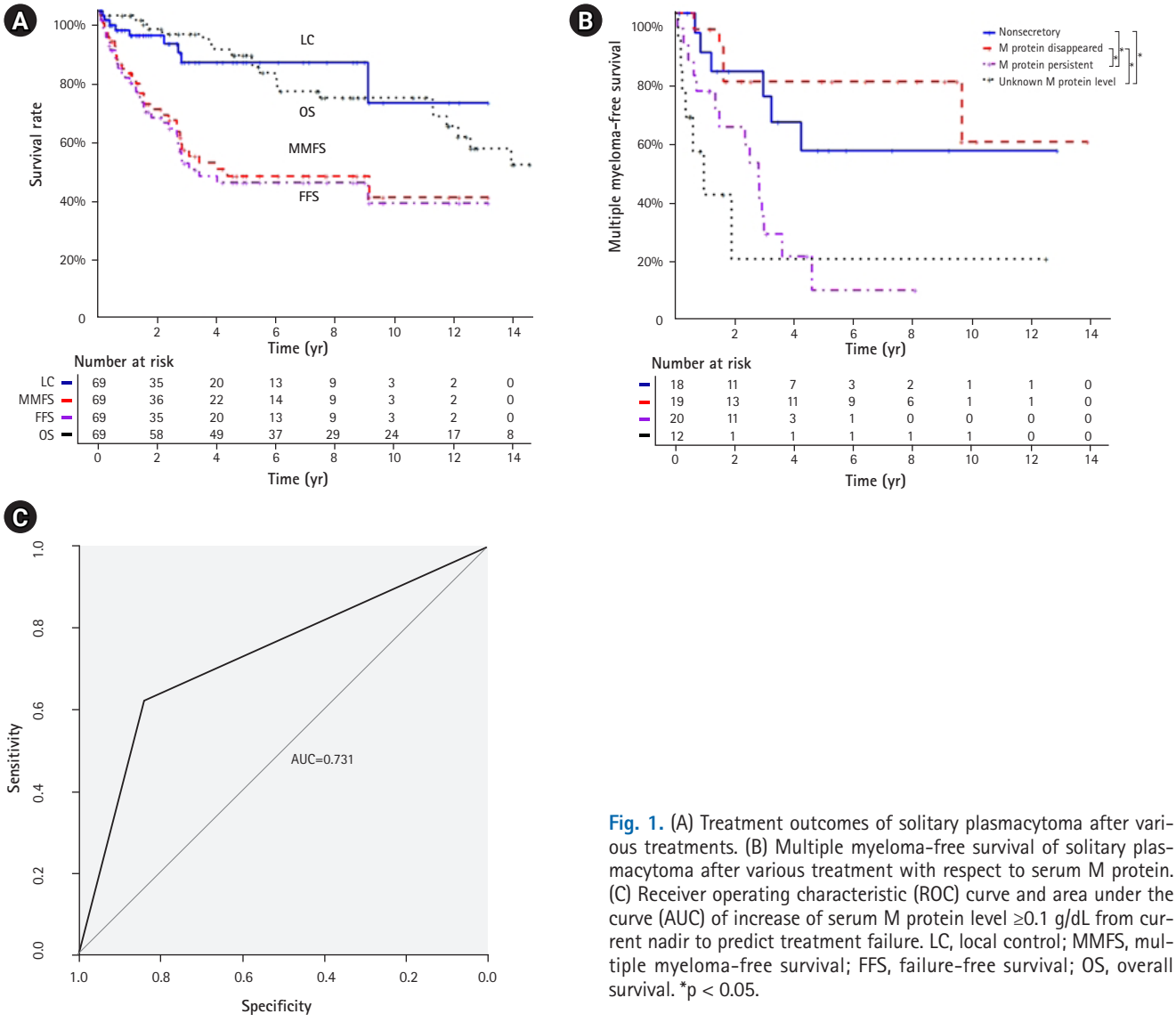


**Fig. 1.** (A) Treatment outcomes of solitary plasmacytoma after various treatments. (B) Multiple myeloma-free survival of solitary plasmacytoma after various treatment with respect to serum M protein. (C) Receiver operating characteristic (ROC) curve and area under the curve (AUC) of increase of serum M protein level ≥0.1 g/dL from current nadir to predict treatment failure. LC, local control; MMFS, multiple myeloma-free survival; FFS, failure-free survival; OS, overall survival. *p < 0.05.

At the time of the analysis, 22 deaths (31.9%) were reported, and 6 patients died from the progression of MM. There were two deaths related to treatments; one from complications after surgical resection and another from side effects of salvage chemotherapy. Five deaths were unrelated to plasmacytoma or treatment and the cause of death of remaining 9 patients was unknown.

## 2. Prognostic factors in patients treated with RT

In the subgroup of patients treated with any treatment that includes RT, tumor location, tumor size, and serum free light chain ratio were significant prognostic factors for MMFS and FFS in the univariate analysis. In the multivariate analysis, SPB (HR = 22.1, p < 0.001), tumor size ≥5 cm (HR = 2.64, p = 0.045), and abnormal serum free light chain ratio (HR = 6.29, p = 0.008) were associated with poor MMFS. For FFS, SPB (HR = 22.7, p < 0.001) and abnormal serum free light chain ratio (HR = 7.38, p = 0.003) were statistically significant adverse prognostic factors. However, there were no significant prognostic factors identified for LC and OS for patients treated with RT. The addition of surgical resection, chemotherapy, or RT dose ≥45 GyEQD2 did not result in significantly improved prognosis.

## 3. Disappearance of serum M protein after treatment as a prognostic factor

At the time of diagnosis, 18 patients were non-secretory. Among the remaining 51 patients who had serum M protein or whose pre-treatment serum M protein level was not evaluated, serum M protein disappeared in 19 patients after a median period of 2.4 months (range, 0.0 to 51.1 months) following treatment. The 5-year MMFS of patients with non-secretory plasmacytoma, disap-


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**Table 2.** Risk factors associated with treatment outcome of solitary plasmacytoma (univariate analysis)

| | Number of patients | 5-yr LC (%) | p-value | 5-yr MMFS (%) | p-value | 5-yr FFS (%) | p-value | 5-yr OS (%) | p-value |
|---|---|---|---|---|---|---|---|---|---|
| Age (yr) | | | | | | | | | |
| < 60 | 32 | 68.7 | 0.150 | 40.8 | 0.680 | 37.3 | 0.550 | 89.5 | 0.320 |
| ≥ 60 | 37 | 94.3 | | 47.4 | | 45.9 | | 81.5 | |
| Sex | | | | | | | | | |
| Male | 41 | 72.5 | 0.130 | 37.4 | 0.220 | 34.0 | 0.098 | 85.8 | 0.190 |
| Female | 28 | 94.4 | | 53.4 | | 53.4 | | 84.2 | |
| Tumor location | | | | | | | | | |
| Extramedullary | 18 | 80.2 | 0.820 | 80.2 | 0.007 | 80.2 | 0.004 | 94.4 | 0.120 |
| Bone | 51 | 82.9 | | 32.1 | | 29.4 | | 81.2 | |
| Tumor size (cm) | | | | | | | | | |
| < 5 | 33 | 83.8 | 0.710 | 70.2 | < 0.001 | 63.7 | 0.001 | 93.2 | 0.076 |
| ≥ 5 | 30 | 87.1 | | 22.6 | | 22.8 | | 74.9 | |
| Anaplastic histology | | | | | | | | | |
| No | 67 | 85.4 | < 0.001 | 45.5 | 0.001 | 43.1 | < 0.001 | 84.6 | 0.260 |
| Yes | 2 | 0.0 | | 0.0 | | 0.0 | | 100.0 | |
| Serum M protein present | | | | | | | | | |
| No | 18 | 90 | 0.470 | 55.7 | 0.220 | 55.7 | 0.130 | 87.1 | 0.650 |
| Yes | 25 | 85.2 | | 27.3 | | 29.2 | | 79.8 | |
| Unknown | 26 | 77.0 | | 47.8 | | 43.1 | | 88.1 | |
| Bence Jones proteinuria | | | | | | | | | |
| Absent | 32 | 88.0 | 0.160 | 37.9 | 0.820 | 39.2 | 0.790 | 85.2 | 0.890 |
| Present | 6 | 100.0 | | 50.0 | | 50.0 | | 100.0 | |
| Unknown | 31 | 74.1 | | 49.1 | | 43.2 | | 82.9 | |
| Serum free light chain ratio | | | | | | | | | |
| Normal | 11 | 100.0 | 0.320 | 67.5 | 0.046 | 67.5 | 0.019 | 90 | 0.910 |
| Abnormal | 11 | 78.8 | | 21.8 | | 18.2 | | 75.0 | |
| Unknown | 47 | 79.6 | | 45.2 | | 43.0 | | 86.3 | |
| Treatment | | | | | | | | | |
| RT alone | 32 | 79.8 | 0.340 | 31.3 | 0.560 | 31.4 | 0.530 | 83.6 | 0.260 |
| Surgery alone | 17 | 72.9 | | 55.8 | | 49.0 | | 94.1 | |
| Surgery + RT | 12 | 100 | | 50.9 | | 50.9 | | 75.0 | |

LC, local control; MMFS, multiple myeloma-free survival; FFS, failure-free survival; OS, overall survival; RT, radiation therapy.

**Table 3.** Risk factors associated with treatment outcome of solitary plasmacytoma (multivariate analysis)

| | LC | | MMFS | | FFS | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Tumor location | | | | | | |
| Extramedullary | - | | Ref. | 0.036 | Ref. | 0.023 |
| Bone | - | | 8.63 (1.15–64.9) | | 10.28 (1.37–76.9) | |
| Size of lesion (cm) | | | | | | |
| < 5 | - | | Ref. | 0.012 | Ref. | 0.043 |
| ≥ 5 | - | | 2.84 (1.26–6.42) | | 2.18 (1.03–4.65) | |
| Anaplastic histology | | | | | | |
| No | Ref. | < 0.001 | Ref. | 0.002 | Ref. | 0.001 |
| Yes | 50.6 (7.01–366) | | 50.9 (4.14–626) | | 66.6 (5.39–822) | |

LC, local control; MMFS, multiple myeloma-free survival; FFS, failure-free survival; HR, hazard ratio; CI, confidence interval.

pearance of serum M protein, persistence of serum M protein, and unknown post-treatment serum M protein level were 55.7%, 78.0%, 10.8%, and 20.8%, respectively (Fig. 1B). The MMFS of non-secretory plasmacytoma patients and patients whose serum M protein disappeared were comparable ($p > 0.05$). Both groups of patients showed significantly superior 5-year MMFS compared to patients who showed persistence of serum M protein and patients whose serum M protein level was not evaluated during follow-up ($p < 0.05$).

### 4. Correlation of disappearance of serum M protein and RT

Among patients who initially had serum M protein, the post-treatment serum M protein level was available from 20 patients. Two patients who did not receive RT showed persistence of serum M protein after treatment, whereas disappearance of serum M protein was observed in 7 patients (38.9%) after RT (Table 3). The rates of disappearance of serum M protein were 25.0% and 66.7% with RT dose < 45 GyEQD2 and ≥ 45 GyEQD2, respectively.

### 5. The increase of serum M protein level as a predictive marker for treatment failure

Next, we tried to predict treatment failures with the level change of serum M protein. Overall, 40 patients were followed up with at least two serum protein electrophoresis tests during follow-up before any treatment failure, defined as local failure and progression to MM. The median value of post-treatment nadir value of serum M protein was 0.0 g/dL (range, 0.0 to 3.2 g/dL). During follow-up, 17 patients experienced an increase of serum M protein level at least once before clinically detected treatment failure. The median of maximum increase of serum M protein from nadir was 0.7 (range, 0.02 to 2.1 g/dL).

Considering the high incidence of non-secretory M protein and low level of serum M protein in solitary plasmacytoma at diagnosis, we evaluated the increase of serum M protein level ≥ 0.1 g/dL from current nadir instead of 0.5 g/dL, which is implemented in MM, to predict treatment failure. The area under the curve (AUC) of the prediction model with this criterion was 0.731 (Table 5, Fig. 1C). Specificity and sensitivity of this model were 84.2% and 61.9%, respectively. The median time to treatment failure from the day serum M protein level increased 0.1 g/dL or more from current nadir was 16.9 months (95% CI, 6.9 months to upper limit not reached).

In addition, three other criteria were evaluated, which are two increases of serum M protein level, two consecutive increases of serum M protein level, and increase of serum M protein above double the value of nadir. The AUC of the prediction models with these criteria were 0.690, 0.662, and 0.614, respectively (Table 5). As the increase of serum M protein level ≥ 0.1 g/dL from current nadir showed highest AUC amongst the four criteria compared, we adopted this criterion to predict treatment failure.

**Table 4.** Correlation of disappearance of serum M protein and radiation therapy

| RT dose[a] | Number of patients | Serum M protein | |
|---|---|---|---|
| | | Disappearance (%) | Persistence (%) |
| No RT | 2 | 0 (0.0) | 2 (100.0) |
| < 45 GyEQD2 | 12 | 3 (25.0) | 9 (75.0) |
| ≥ 45 GyEQD2 | 6 | 4 (66.7) | 2 (33.3) |

RT, radiation therapy; EQD2, equivalent dose in 2-Gy fractions at $\alpha/\beta$ of 10.
[a]One patient with unknown dose excluded.

## Discussion and Conclusion

In this study, we evaluated the prognostic value of serum M protein level at diagnosis and its level change or conversion during follow-up to assess treatment response and predict treatment failures of solitary plasmacytoma.

Prognostic factors with contradictory prognostic values for solitary plasmacytoma were demonstrated in previous studies due to different treatment profiles and small number of patients included in each study. Although local control was excellent in this study and was also consistent with that of previous studies, progression to MM remained to be the main obstacle for failure-free survival as observed in Fig. 1A. In this study, SPB and tumor size ≥ 5 cm were associated with poor MMFS and FFS, which is consistent with the results of previous studies [3,5,8,9,19,20]. Older age [3,5,19–21], the abnormal post-treatment free light chain ratio [12], the pres-

**Table 5.** Correlation of various increases of serum M proteins with treatment failure

| | Number of patients (%) | Sensitivity (%) | Specificity (%) | AUC | Median time to treatment failure (mo) |
|---|---|---|---|---|---|
| Increase ≥ 0.1 g/dL from current nadir | 16 (40.0) | 61.9 | 84.2 | 0.731 | 16.9 |
| Two increases | 13 (37.1) | 55.6 | 82.4 | 0.690 | 20.8 |
| Two consecutive increases | 12 (34.3) | 50.0 | 82.4 | 0.662 | 17.4 |
| Increase double above nadir | 9 (22.5) | 33.3 | 89.5 | 0.614 | 4.0 |

AUC, area under the curve.


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ence of serum M protein at diagnosis [5] and after treatment [12] were also suggested to be associated with poor prognosis. Warsame et al. [22] reported clonal plasma cells in BM, presence of urine Bence Jones protein, and higher RT dose as adverse prognostic factors for progression-free survival.

In addition to SPB and tumor size ≥5 cm, anaplastic plasmacytoma was associated with poor LC, MMFS, and FFS. Anaplastic plasmacytoma is an extremely rare type of plasmacytoma which can develop in patients with immunosuppression and combined Epstein-Barr virus infection [23]. However, because of its rarity the clinical course of anaplastic plasmacytoma is unknown. In this study, two patients of anaplastic plasmacytoma were included and they showed rapid local failure and progression to MM. However, both patients survived more than 10 years. It seems that anaplastic plasmacytoma shows rapid progression but does not result in poor overall survival, but the clinical course of anaplastic plasmacytoma needs to be investigated with larger number of patients.

In this study, patients with non-secretory plasmacytoma and patients whose serum M protein disappeared after treatment showed superior MMFS compared to patients who had persistent serum M protein after treatment. However, the prognostic value of serum M protein level at diagnosis is controversial. Non-secretory plasmacytoma showed better MMFS in the study by Reed et al. [5], whereas the opposite result showing that non-secretory plasmacytoma is associated with worse MMFS and cause-specific survival was also reported [13,14]. In contrast, the persistence of M protein after treatment is uniformly reported to be associated with poor MMFS [12–14], which was also observed in this current study. Moreover, we showed the usefulness of the increase of serum M protein level ≥0.1 g/dL from current nadir for predicting treatment failures. Therefore, it would be reasonable to follow-up patients, who initially had serum M protein or whose pre-treatment serum M protein level was not evaluated, with a regular serum protein electrophoresis test along with radiologic examinations until the serum M protein disappears. In addition, even if patients had non-secretory disease or their serum M protein disappeared, a regular follow-up with serum protein electrophoresis would be needed in order to make earlier detection and salvage treatment possible.

Immunofixation and free light chain ratio are another tests to evaluate serum M protein. It has been reported that 9.7% of normal serum protein electrophoresis showed positive immunofixation result [24] and therefore, immunofixation could be a good complementary test when combined with serum protein electrophoresis during follow-up. Abnormal serum free light chain ratio was a significant prognostic factor in patients who were treated with RT in our study and in a previous study [12]. Considering this, serum free light chain ratio could be another potential predictive biomarker to be investigated and utilized.

RT has been known as the treatment of choice for solitary plasmacytoma [15,25,26] with evidences from retrospective studies showing improved LC [3], disease-free survival [3], and OS [2] with RT. Regarding the dose of RT, higher doses were recommended for SEP [27] and larger tumors [19], although no definite dose-response relationship for RT >30 Gy was observed in another study [3]. In this study, we also could not find a definite dose-response relationship. However, RT ≥45 GyEQD2 seemed to increase the rates of disappearance of serum M protein, which can be interpreted as good treatment response, although the number of patients were insufficient to show definite relationship.

In this study, since solitary plasmacytoma without evidence of MM is very rare in nature, we could find only a small number of patients. Patients who were incidentally diagnosed as solitary plasmacytoma after surgical resection lacked the pre-treatment work-up for solitary plasmacytoma as shown in Supplementary Table S2. Therefore, our definition of disappearance of serum M protein included patients whose initial serum M protein level was not evaluated when predicting the prognosis with respect to serum M protein level. However, considering that it is often the case that solitary plasmacytoma is incidentally diagnosed after surgery, as it was in this study, it would be still meaningful to include patients whose initial serum M protein was not evaluated and predict their prognosis. Also, the data of proportion of clonal plasma cells in the bone marrow was not available in 46.4% of the patients and therefore, we could not show any prognostic difference between solitary plasmacytoma and solitary plasmacytoma with minimal marrow involvement according to the IMWG criteria. However, with long-term follow-up data, we could derive a meaningful conclusion regarding the clinical value of serum M protein level, although further studies with larger number of patients are needed for validation.

In conclusion, we found that patients who eventually showed persistent serum M protein after treatment had worse prognosis compared to those whose serum M protein disappeared or initially had non-secretory disease. Also, the increase of serum M protein level ≥0.1 g/dL from current nadir was predictive of treatment failure. Therefore, we recommend a regular follow-up with serum protein electrophoresis after the treatment of solitary plasmacytoma to assess treatment response and predict treatment failure. Also, closer follow-up with serum protein electrophoresis is needed for patients who initially had serum M protein or whose serum M protein level was not evaluated.

## Conflict of Interest

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

## Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2019.00570

Table S1. Risk factors associated with treatment outcome of solitary plasmacytoma treated with RT (univariate analysis)

Table S2. Characteristic of the patients according to their treatments

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# Dosimetric comparison of coplanar and non-coplanar volumetric-modulated arc therapy in head and neck cancer treated with radiotherapy

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**Purpose:** To evaluate the dosimetric variations in patients of head and neck cancer treated with definitive or adjuvant radiotherapy using optimized non-coplanar (ncVMAT) beams with coplanar (cVMAT) beams using volumetric arc therapy.

**Materials and Methods:** Twenty-two patients of head and neck cancer that had received radiotherapy using VMAT in our department were retrospectively analyzed. Each of the patients was planned using coplanar and non-coplanar orientations using an optimized couch angle and fluences. We analyzed the Conformity Index ($CI_{RTOG}$), Dose Homogeneity Index (DHI), Heterogeneity Index ($HI_{RTOG}$), low dose volume, target and organs-at-risk coverage in both the plans without changing planning optimization parameters.

**Results:** The prescription dose ranged from 60 Gy to 70 Gy. Using ncVMAT, $CI_{RTOG}$, DHI and $HI_{RTOG}$, and tumor coverage ($ID_{95\%}$) had improved, low dose spillage volume in the body $V_{5Gy}$ was increased and $V_{10Gy}$ was reduced. Integral dose and intensity-modulated radiation therapy factor had increased in ncVMAT. In the case of non-coplanar beam arrangements, maximum dose ($D_{max}$) of right and left humeral head were reduced significantly whereas apex of the right and left lung mean dose were increased.

**Conclusion:** The use of ncVMAT produced better target coverage and sparing of the shoulder and soft tissue of the neck as well as the critical organ compared with the cVMAT in patients of head and neck malignancy.

**Keywords:** Head and neck neoplasm, Intensity-modulated radiotherapy

## Introduction

Head and neck cancers form about 30% of the total malignancies registered in a year in India. More than 400,000 new cases are diagnosed per annum [1,2]. Radiotherapy plays a major role in the management of this diverse spectrum of malignancies in the definitive, adjuvant and palliative setting. The major proportion of patients in India present in the advanced stages of the disease which further cements the position of radiotherapy in the plan of management. In the radical scheme of treatment of head and cancers, volumetric-modulated arc therapy (VMAT) was found to provide similar conformity and better homogeneity and organa-at-risk (OAR) sparing when compared to intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy [3-7]. Currently, considering the anatomical complexity, target coverage and OARs sparing, the use of non-coplanar beam arrangements with possible arc gantry geometry showed improvement over coplanar beam arrangements from various perspectives [8-10].

Owing to the normal anatomy of the human body, irradiation with coplanar VMAT (cVMAT) is different from non-coplanar VMAT

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(ncVMAT) due to longer photon path length of the coplanar beams passing through the shoulders and soft tissue of the neck to reach the target. The goal of radiotherapy is to maximize the dose to the primary site with adequate margins while minimizing dose to the nearby structures. Dosimetric comparisons between ncVMAT and cVMAT treatment plans showed clinically significant dosimetric improvements through an optimization process that could potentially allow substantial dose escalation, and improved local tumor control without exceeding critical OARs dose limits decided for the clinical plans for patients on conventional C-arm linear accelerators [11-13].

With this background, we undertook a retrospective analysis of the patients of head and neck cancer treated in our center to study the dosimetric differences between the two commonly employed planning techniques, namely, coplanar and non-coplanar VMAT planning.

## Materials and Methods

### 1. Patients

Plans of 22 patients of head and neck cancer that had received radiotherapy using VMAT in our department during 2018–2019 were retrospectively analyzed. All of them received definitive or adjuvant radiation therapy with curative intent up to a dose of 70 Gy delivered based on their clinical-stage, over 6–7 weeks (5 fractions per week) by a clinical linear accelerator (LINAC) (Elekta Versa HD; Elekta, Crawley, UK), following the International Commission on Radiation Units and Measurements (ICRU) recommendations, either alone or in combination with concomitant chemotherapy (chemoradiation).

### 2. Simulation and contouring

Each patient was positioned supine on a 16-slice computed tomography (CT) simulator (Optima 580; GE Healthcare, Waukesha, WI, USA) using a whole-body board (MacroMedics, Waddinxveen, The Netherlands) with a thermoplastic mask covering the head and shoulders and helical scans of 2.5 mm slice thickness were acquired from vertex to carina while the patient was breathing freely. The contours were done in the Monaco SIM (V5.11.02; Elekta CMS, Sunnyvale, CA, USA) contouring workstation.

Following the ICRU guidelines, the planning target volumes (PTV) of each of the patients included the primary with the lower limit of PTV including level IVA. The target volume delineation was done according to standard institutional protocol. The gross tumor volume to clinical target volume (CTV) was expanded by 1 cm in the low risk (CTV-low) along with the areas that are at low risk for the subclinical spread and by 0.5 cm along with the areas at high risk for the subclinical spread in high risk (CTV-high). The CTV to PTV expansion was 0.3 cm in all the cases. The OARs analyzed were bilateral humeral heads, bilateral lung apices, bilateral brachial plexuses, bilateral parotid glands, brainstem, and spinal cord. All the organs were contoured according to the Radiation Therapy Oncology Group (RTOG) atlas for normal tissue contouring [14]. The lung apices were contoured to a level that is 4 cm beyond the lowest level of PTV for uniformity among patients.

### 3. Dose prescription

Eleven patients were treated using the standard simultaneous integrated boost (SIB) technique. In this population, patients were prescribed up to a total dose of 70 Gy to the PTV-high risk and 54 Gy to the PTV-low risk with a maximum of 35 fractions.

Another set of 11 patients were treated using sequential (Phase I and Phase II) technique, in which the patients were prescribed up to 70 Gy in 35 fractions at 2 Gy per fraction.

In the sequential technique, all the patients were planned with both coplanar and non-coplanar beam arrangements in Phase I with dose ranging from 46 Gy to 60 Gy and the remaining dose was delivered in the next phase. In Phase II, PTV was located most of the time above the shoulder and the application of non-coplanar beams was not taken as a consideration. For this reason, we had taken only the sequential based Phase I and the dosimetric comparison had been reported between cVMAT and ncVMAT plans. Patient characteristics and dose prescriptions are described in Table 1.

### 4. Radiotherapy planning and dosimetry

All patients were planned using volumetric arc therapy treatment plans designed on Monaco (V5.11.02, Elekta CMS) treatment planning system with 6 MV flat photon beam which has maximum dose rate of 600 cGy/min at $D_{max}$. Each of the patients was planned using coplanar and non-coplanar orientations using an optimized couch angle and fluences. Both the cVMAT and ncVMAT plans were qualitatively evaluated for each patient and the dosimetric data was taken from the dose-volume histogram (DVH) data which represents the whole dose-volume information in a two-dimensional single curve.

Each of the non-coplanar beam angles in our approach was associated with achievable gantry-couch-patient clearance. Non-coplanar plans were generated using two non-coplanar beam arrangements with double arc VMAT in which, the gantry angles were chosen from 0° to +180° with 350° couch angle for the first beam arrangement in the clockwise direction and 0° to -180° with 10° couch angle in the counterclockwise direction for the second beam arrangement with an increment of 20°. For ncVMAT, we had

**Table 1.** Patients characteristics

| | Patient# | Age (yr) | Sex | Primary | Stage | Intent | Dose fractionation | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | PTV-high | PTV-low | Phase I | Phase II |
| SIB | 1 | 50 | M | Tongue | IVB | Adjuvant | 70 Gy in 35 fx | 54 Gy in 35 fx | - | - |
| | 2 | 43 | M | Hypo-pharynx | IVA | Definitive | 70 Gy in 35 fx | 54 Gy in 35 fx | - | - |
| | 3 | 57 | M | Cheek | IVB | Adjuvant | 70 Gy in 35 fx | 54 Gy in 35 fx | - | - |
| | 4 | 51 | M | Base of tongue | II | Definitive | 70 Gy in 33 fx | 54 Gy in 33 fx | - | - |
| | 5 | 73 | M | Base of tongue | IVA | Definitive | 66 Gy in 33 fx | 54 Gy in 33 fx | - | - |
| | 6 | 73 | F | Base of tongue | IVA | Definitive | 66 Gy in 33 fx | 54 Gy in 33 fx | - | - |
| | 7 | 51 | M | Base of tongue | IVA | Definitive | 66 Gy in 33 fx | 54 Gy in 33 fx | - | - |
| | 8 | 61 | F | Tongue | III | Adjuvant | 66 Gy in 30 fx | 54 Gy in 30 fx | - | - |
| | 9 | 71 | M | Hypo-pharynx | III | Definitive | 66 Gy in 30 fx | 54 Gy in 30 fx | - | - |
| | 10 | 75 | F | Base of tongue | III | Definitive | 66 Gy in 30 fx | 54 Gy in 30 fx | - | - |
| | 11 | 63 | M | Tongue | IVA | Adjuvant | 60 Gy in 30 fx | 54 Gy in 30 fx | - | - |
| Sequential | 12 | 55 | M | Soft palate | IVA | Adjuvant | - | - | 54 Gy in 27 fx | 12 Gy in 6 fx |
| | 13 | 76 | M | Tongue | IVA | Adjuvant | - | - | 54 Gy in 27 fx | 12 Gy in 6 fx |
| | 14 | 59 | M | Oropharynx | IVA | Adjuvant | - | - | 54 Gy in 27 fx | 16 Gy in 8 fx |
| | 15 | 42 | F | Base of tongue | III | Definitive | - | - | 50 Gy in 25 fx | 16 Gy in 8 fx |
| | 16 | 31 | M | Tongue | IVA | Adjuvant | - | - | 46 Gy in 23 fx | 14 Gy in 7 fx |
| | 17 | 43 | F | Base of tongue | IVA | Definitive | - | - | 46 Gy in 23 fx | 14 Gy in 7 fx |
| | 18 | 33 | M | Cheek | IVB | Adjuvant | - | - | 54 Gy in 27 fx | 16 Gy in 8 fx |
| | 19 | 24 | F | Nasopharynx | IVA | Definitive | - | - | 60 Gy in 30 fx | 10 Gy in 5 fx |
| | 20 | 46 | M | Cheek | IVB | Adjuvant | - | - | 54 Gy in 27 fx | 16 Gy in 8 fx |
| | 21 | 62 | F | Upper alveolus | II | Adjuvant | - | - | 54 Gy in 27 fx | 16 Gy in 8 fx |
| | 22 | 49 | M | Tonsil | II | Definitive | - | - | 54 Gy in 27 fx | 16 Gy in 8 fx |

PTV, planning target volume; SIB, simultaneous integrated boost.

used partial arcs with a value of ±10° couch angle to avoid the shoulder region. The maximum number of control points per arc was selected as 180 to allow sufficient modulation and acceptable duration of the optimization with a minimum segment width of 1 cm. The collimator angle was selected typically according to beam alignment to avoid tongue-and-groove effects and to cover the entire PTV region.

Similarly, coplanar plans were generated using single beam arrangement with double arc VMAT in which the gantry was chosen from +180° to -180° with 0° couch angle and 0° collimator angle in a counterclockwise direction or clockwise direction with a same increment angle 20°. All the other planning parameters were as same as ncVMAT plans. The typical beam arrangements for an example case is illustrated in Fig. 1.

The optimization technique used in VMAT is segment shape optimization (SSO) where the target dose rate will be auto-selected by the system itself. Similar to the sliding window technique, VMAT follows sweep sequencer and create segments and optimizes to achieve the desired dose distribution to target and OARs. The PTVs were reduced to 1 mm below the skin surface. Treatment plans were optimized with the same dose constraints for OAR. For PTV coverage, described by the ICRU Report 83, 95% of PTV volume should receive 95% of the prescribed dose.

All the VMAT plans were created and calculated using the Monte Carlo (v1.6) dose calculation algorithm based on cost functions (achieving a dose distribution to the given value) with a grid size of 0.3 cm and 2% calculation uncertainty based on the beam data of our LINAC equipped with 160 leaves Agility MLC of 5 mm leaf thickness.

The Conformity Index ($CI_{RTOG}$) [15-17], isodose line covering 95% of the volume within PTV ($ID_{95\%}$), Dose Homogeneity Index (DHI) [15-17], Homogeneity Index ($HI_{RTOG}$) [15-17], conformity number (CN) [15-18], low dose volume and OAR coverage in both the plans were analyzed. Total monitor units (MU) per fraction, IMRT ratio, i.e., total MU per cGy prescription dose [19-23], and the integral dose to patients [24,25] were noted and compared. The dose covering a percentage of the structure's volume ($D_{\%}$) and the volume of the structure receiving a certain dose ($V_{\%}$ or $V_{Gy}$) were used for dosimetric evaluation and planning purposes. For low dose volume, $V_{5Gy}$, $V_{10Gy}$, $V_{20Gy}$, and $V_{30Gy}$ were analyzed and compared. The OAR specific variables assessed were $D_{max}$ and $D_{15\%}$ for the humeral heads, $D_{max}$ and $D_{5\%}$ for the brachial plexuses, $D_{mean}$ for the lung


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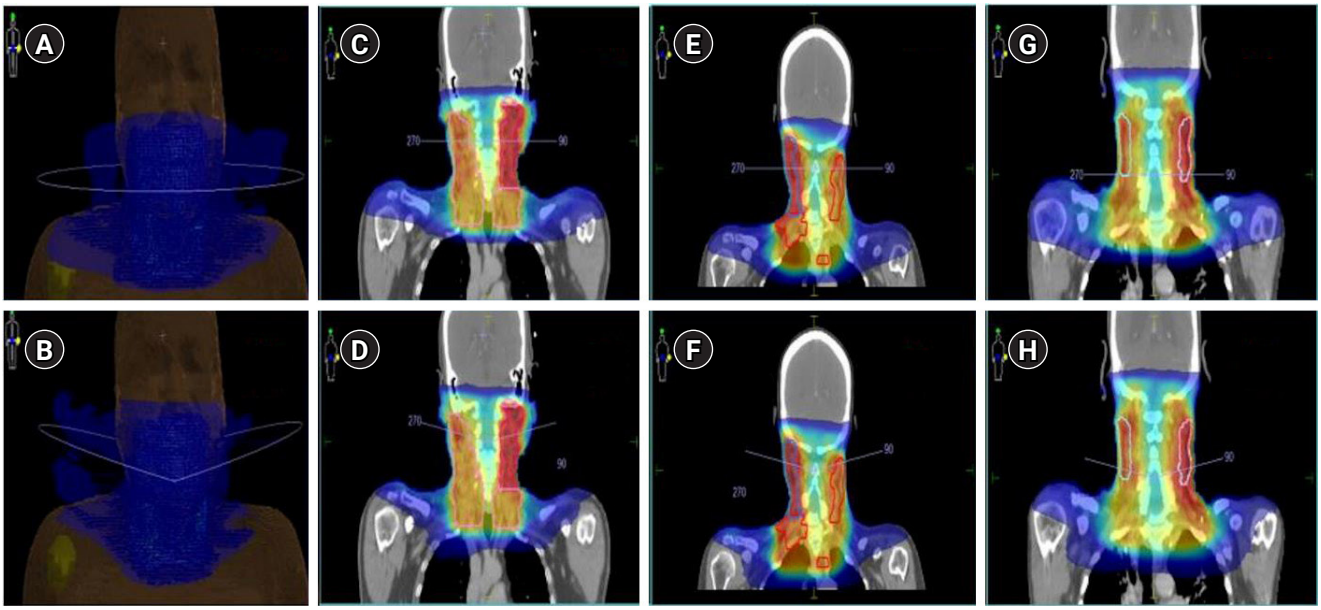


**Fig. 1.** The typical beam arrangements of coplanar VMAT plan (A) and non-coplanar VMAT plan (B) for an example case with a dose color wash. The typical dose distribution of both the beam arrangements in coronal planes for three example cases with a color-wash display ranging from 5 Gy to 70 Gy where (C), (E), and (G) are the three coronal planes for coplanar beam arrangements and (D), (F), and (H) are the same three coronal planes for non-coplanar beam arrangements, respectively.

apices, $D_{mean}$ and $D_{50\%}$ for the parotids and $D_{max}$ for both the spinal cord and brainstem.

### 5. Statistical analysis

Statistical comparison of planning parameters, dose to the OARs and low dose volumes between cVMAT and ncVMAT plans were performed using SPSS, a data analysis software. As all the variables are quantitative, each of them is denoted by their respective means with standard deviation or with their ranges and analyzed statistically using the Wilcoxon matched paired signed-rank test. Evaluation of the level of significance of the observed difference between the dose-volume metrics had been performed and $p < 0.05$ was considered as statistically significant.

## Results

Of the 22 patients with a median age of 53 years analyzed, 11 patients were treated with adjuvant intent and 11 with definitive intent, details regarding the prescription dose and stage are tabulated in Table 1. In Tables 2 and 3, the DVH parameters for the PTV and OARs are mentioned with both the types of beam arrangements in VMAT plans for all the cases.

For the single PTV in phase-I planned with sequential technique, there was no significant difference in the values of $CI_{RTOG}$, CN, $ID_{95\%}$, DHI, and $HI_{RTOG}$. On the contrary, significant differences were found in the SIB technique. In the PTV-high risk, the average values for the $CI_{RTOG}$, CN, $ID_{95\%}$, and DHI were reduced by 4.2%, 2.4%, 2.3%, and 2.2%, respectively, but $HI_{RTOG}$ was increased by 1.7% in cVMAT. Similarly in the PTV-low risk, the average values for the $CI_{RTOG}$, $ID_{95\%}$, and DHI were reduced by 2.1%, 2.4% and 2.4% and $HI_{RTOG}$ was increased by 2.2% in cVMAT. The monitor units utilized in the plans were significantly higher in the non-coplanar sequential plans but the same could not achieve statistical significance in the SIB technique. Treatment delivery time was significantly longer for non-coplanar plans in both sequential and SIB modalities. For all the cases, the average value of the IMRT ratio in the cVMAT plans was significantly reduced by 5.4%.

Upon analysis of DVH parameters of the OARs achieved, it was noted that the $D_{max}$ of the bilateral humeral head, $D_{max}$ of right brachial plexus, and $D_{50\%}$ of the left parotid were significantly higher in the cVMAT plans. At the same time, $D_{mean}$ of the bilateral lung apices was significantly lower in the cVMAT plans. For the right humeral head, the average value of $D_{max}$ was increased by 50.7% in the sequential plans and 48.3% in the SIB plan, respectively. Similarly, for the left humeral head, the average value of $D_{max}$ was increased by 42.2% in the sequential plans and 21.1% in the SIB plan, respectively. In the right brachial plexus, the average value of $D_{max}$ was increased by 1.1% in the sequential plans and 1.2% in the SIB plan, respectively. In the left parotid, the average value of $D_{50\%}$ was increased by 2% in the sequential plans and 5.7% in the SIB

**Table 2.** Summary of the quantitative analysis of DVH of the target volumes for the two techniques

| | Sequential | | | SIB | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | PTV in phase-I | | | PTV-high | | | PTV-low | | |
| | ncVMAT | cVMAT | p-value | ncVMAT | cVMAT | p-value | ncVMAT | cVMAT | p-value |
| CIRTOG | 0.95 ± 0.02 | 0.93 ± 0.02 | 0.159 | 0.96 ± 0.02 | 0.92 ± 0.05 | 0.007* | 0.97 ± 0.02 | 0.95 ± 0.02 | 0.007* |
| CN | 0.75 ± 0.03 | 0.75 ± 0.04 | 0.435 | 0.83 ± 0.06 | 0.81 ± 0.06 | 0.031* | 0.36 ± 0.15 | 0.36 ± 0.15 | 0.317 |
| $ID_{95\%}$ | 94.2 ± 0.99 | 93.66 ± 1.29 | 0.125 | 95.40 ± 1.12 | 93.23 ± 1.94 | 0.006* | 97.65 ± 2.01 | 95.30 ± 1.91 | 0.003* |
| DHI | 0.91 ± 0.01 | 0.90 ± 0.01 | 0.020* | 0.92 ± 0.01 | 0.90 ± 0.02 | 0.005* | 0.84 ± 0.04 | 0.82 ± 0.04 | 0.017* |
| $HI_{RTOG}$ | 1.18 ± 0.02 | 1.19 ± 0.03 | 0.11 | 1.16 ± 0.02 | 1.18 ± 0.03 | 0.028* | 1.34 ± 0.08 | 1.37 ± 0.08 | 0.007* |
| MU | 900.02 ± 94.31 | 860.67 ± 76.51 | 0.003* | - | - | - | 921.12 ± 128.83 | 860.55 ± 86.71 | 0.110 |
| Delivery time (min) | 11.5 ± 2.23 | 10.69 ± 2.33 | 0.042* | - | - | - | 12 ± 2.12 | 11.28 ± 2.04 | 0.043* |
| IMRT ratio (overall) | | | | 4.48 ± 0.55 | 4.24 ± 0.43 | 0.004* | | | |

Values are presented as mean ± standard deviation.
DVH, dose-volume histograms; PVT, planning target volume; ncVMAT, non-coplanar volumetric-modulated arc therapy; cVMAT, coplanar VMAT; $CI_{RTOG}$ , Conformity Index (according to RTOG); CN, conformity number; $ID_{95\%}$, isodose line covering 95% volume of the target; DHI, Dose Homogeneity Index; $HI_{RTOG}$, Homogeneity Index (according to RTOG); SIB, simultaneous integrated boost; MU, monitor unit; IMRT, intensity-modulated radiation therapy.
*$p < 0.05$.

**Table 3.** Summary of the quantitative analysis of DVH of the organs-at-risk and low dose volumes in the patients for the two techniques

| Parameter | | Sequential | | | SIB | | |
|---|---|---|---|---|---|---|---|
| | | ncVMAT | cVMAT | p-value | ncVMAT | cVMAT | p-value |
| Rt. Humeral head | $D_{15\%}$ (Gy) | 2.91 ± 0.88 | 3.62 ± 2.12 | 0.374 | 5.96 ± 3.77 | 7.79 ± 4.59 | 0.182 |
| | $D_{max}$ (Gy) | 4.34 ± 1.57 | 6.54 ± 3.03 | 0.008* | 9.07 ± 5.74 | 13.45 ± 5.58 | 0.007* |
| Lt. Humeral head | $D_{15\%}$ (Gy) | 3.97 ± 1.18 | 4.30 ± 1.50 | 0.534 | 5.71 ± 2.32 | 6.57 ± 4.14 | 0.374 |
| | $D_{max}$ (Gy) | 5.74 ± 1.53 | 8.16 ± 2.66 | 0.050* | 8.99 ± 4.70 | 10.89 ± 5.24 | 0.050* |
| Lt. Brachial plexus | $D_{max}$ (Gy) | 56.15 ± 4.40 | 56.42 ± 4.09 | 0.374 | 64.22 ± 4.95 | 64.74 ± 4.81 | 0.328 |
| | $D_{5\%}$ (Gy) | 53.75 ± 4.27 | 53.85 ± 4.24 | 0.45 | 59.95 ± 4.31 | 60.31 ± 4.37 | 0.328 |
| Rt. Brachial plexus | $D_{max}$ (Gy) | 55.76 ± 4.05 | 56.37 ± 4.25 | 0.045* | 63.15 ± 4.45 | 63.89 ± 4.11 | 0.041* |
| | $D_{5\%}$ (Gy) | 53.56 ± 4.08 | 53.99 ± 4.36 | 0.059 | 59.72 ± 4.23 | 59.94 ± 4.06 | 0.594 |
| Lt. Lung apex | $D_{mean}$ (Gy) | 17.04 ± 3.69 | 15.13 ± 4.14 | 0.003* | 18.24 ± 3.99 | 16.88 ± 3.56 | 0.040* |
| Rt. Lung apex | $D_{mean}$ (Gy) | 16.14 ± 3.16 | 15.14 ± 3.67 | 0.004* | 18.68 ± 3.90 | 17.02 ± 3.70 | 0.005* |
| Spinal cord | $D_{max}$ (Gy) | 35.03 ± 2.58 | 35.05 ± 2.92 | 0.374 | 40.53 ± 1.78 | 40.45 ± 1.54 | 0.657 |
| Brainstem | $D_{max}$ (Gy) | 34.06 ± 5.69 | 33.94 ± 4.13 | 0.534 | 40.43 ± 5.72 | 39.29 ± 6.42 | 0.445 |
| Lt. Parotid | $D_{mean}$ (Gy) | 21.59 ± 3.64 | 21.85 ± 3.50 | 0.092 | 27.98 ± 7.37 | 28.39 ± 8.02 | 0.534 |
| | $D_{50\%}$ (Gy) | 15.80 ± 5.77 | 16.11 ± 5.40 | 0.002* | 22.45 ± 10.74 | 23.74 ± 11.59 | 0.004* |
| Rt. Parotid | $D_{mean}$ (Gy) | 21.40 ± 2.39 | 21.76 ± 2.67 | 0.241 | 31.71 ± 9.01 | 31.52 ± 9.01 | 0.929 |
| | $D_{50\%}$ (Gy) | 14.12 ± 2.09 | 14.68 ± 2.92 | 0.203 | 28.83 ± 16.16 | 28.96 ± 15.59 | 1.000 |
| Integral dose (Gy.L) | | 113.51 ± 15.78 | 110.77 ± 14.52 | 0.004* | 129.13 ± 21.02 | 126.35 ± 21.20 | 0.004* |
| Low dose volume | $V_{5Gy}$ (mL) | 3,751.52 ± 359.40 | 3,647.82 ± 375.82 | 0.033* | 4,104.14 ± 692.25 | 3,963.03 ± 732.43 | 0.010* |
| | $V_{10Gy}$ (mL) | 2,909.34 ± 297.48 | 2,943.97 ± 288.88 | 0.043* | 3,133.32 ± 568.04 | 3,217.23 ± 595.92 | 0.040* |
| | $V_{20Gy}$ (mL) | 2,181.05 ± 300.21 | 2,176.84 ± 288.75 | 0.424 | 2,304.10 ± 417.52 | 2,298.86 ± 404.26 | 0.929 |
| | $V_{30Gy}$ (mL) | 1,584.82 ± 250.35 | 1,578.64 ± 250.32 | 1.000 | 1,704.40 ± 327.61 | 1,717.65 ± 326.45 | 0.286 |

Values are presented as mean ± standard deviation.
DVH, dose-volume histograms; SIB, simultaneous integrated boost; ncVMAT, non-coplanar volumetric-modulated arc therapy; cVMAT, coplanar VMAT; $D_{\%}$, the dose covering a percentage of the structure's volume; $D_{max}$ and $D_{mean}$, the maximum point dose and mean dose for a volume; $V_{Gy}$, the volume of the structure receiving a certain dose.
*$p < 0.05$.


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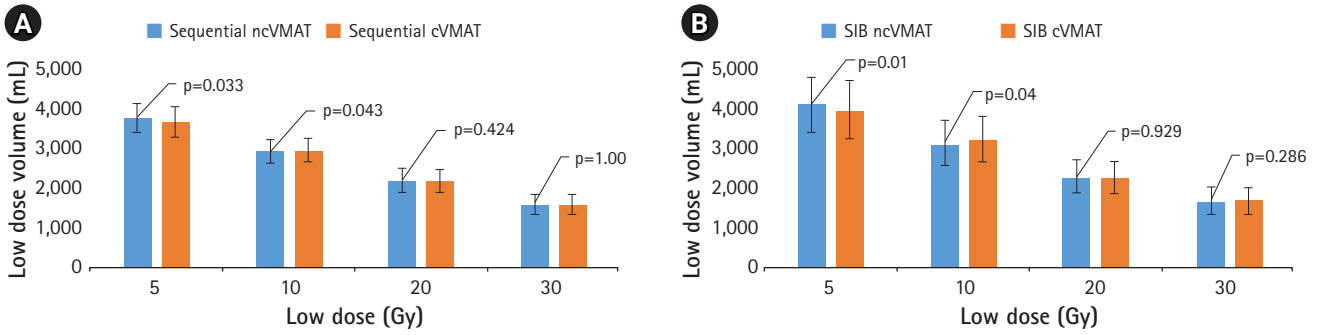


**Fig. 2.** Summary of the average values of volume encompassed by the low doses in the healthy body tissues for all the cases: (A) non-coplanar VMAT (ncVMAT) and coplanar VMAT (cVMAT) treatment plans for sequential based Phase I and (B) ncVMAT and cVMAT treatment plans for SIB technique. VMAT, volumetric-modulated arc therapy; SIB, simultaneous integrated boost.

plan, respectively. On the contrary, for left lung apex, the average value of $D_{mean}$ was simultaneously reduced by 11.2% in the sequential plans and 7.5% in the SIB plan, respectively. Similarly, for the right lung apex, the average value of $D_{mean}$ was simultaneously reduced by 6.2% in the sequential plans and 8.9% in the SIB plan, respectively. The rest of the dose parameters of the OARs assessed failed to show a statistically significant difference between the two types of plans. Fig. 1 depicts the typical dose distribution of both the beam arrangements in coronal planes for three example cases with a color-wash display ranging from 5 Gy to 70 Gy. The analysis of the volume of the healthy tissue of body receiving low doses of the tune of 5 Gy, 10 Gy, 20 Gy, and 30 Gy revealed that there was a statistically significant increase in $V_{5Gy}$ by 2.8% in sequential and 3.4% in SIB techniques when planned on ncVMAT. Conversely, it showed a significant decrease in $V_{10Gy}$ by 1.2% in sequential and 2.7% in SIB techniques when planned on ncVMAT. The difference was not significant for higher doses like $V_{20Gy}$ and $V_{30Gy}$. In Fig. 2, the summary of the average values of volume encompassed by the low doses in the healthy body tissues for all the cases was depicted clearly. From the DVH metrics of all the cases, the average value of integral doses significantly reduced by 2.4% in sequential and 2.2% in SIB techniques when planned by cVMAT.

From the quantitative analysis of Fig. 3, it was noted the dose fall-off beyond the target region was similar for all the datasets. In our study, the decrease in the average value of total volume (V) encompassed was following a logarithmic pattern for the increase in dose (D) value. For evaluation of the rate of dose fall-off beyond PTV, we have taken ln(1/V) vs. ln(D). From Fig. 4, it is represented that ln(1/V) vs. ln(D) was following a straight line for all the different datasets. The gradient or slope was calculated from the graphs and the value of the gradient were 0.4647 and 0.4540 for ncVMAT and cVMAT (reduced by 2.3%) in the sequential techniques and 0.4778 and 0.4606 for ncVMAT and cVMAT (reduced by 3.6%) in SIB techniques, respectively.

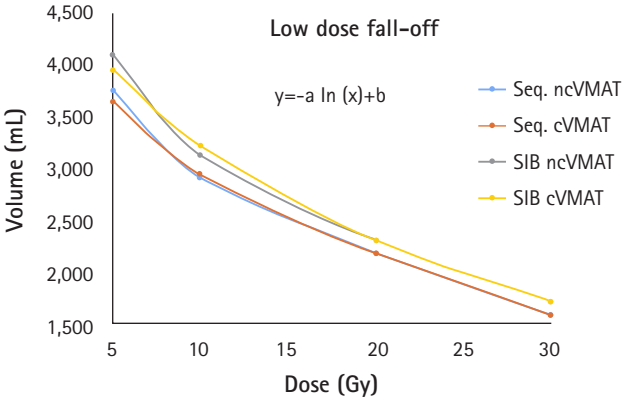


**Fig. 3.** The dose fall-off beyond the target region for all the cases planned with both the sequential and SIB technique for coplanar (cVMAT) and non-coplanar (ncVMAT) plans. Here, the y-axis represents the volume encompassed in cc and the x-axis represents the dose in Gy. For all the cases, in our study, the pattern of dose fall-off is best fitted by logarithmic curves with the equation written below y = -a ln(x) + b, where a and b are constant values, respectively. VMAT, volumetric-modulated arc therapy; SIB, simultaneous integrated boost.

## Discussion and Conclusion

Current treatment modalities introduced new radiotherapy techniques which improved the quality of treatment. IMRT is a widely used technique for head and neck cancers delivering a non-uniform dose from multiple angles to create a very conformal dose to targets with minimal complication to surrounding OARs [26,27]. In arc-based IMRT (VMAT), the intensity is modulated generating dose fluences throughout the gantry rotation with the aid of variable speed of gantry, MLC movements and dose rate with shorter delivery time than IMRT.

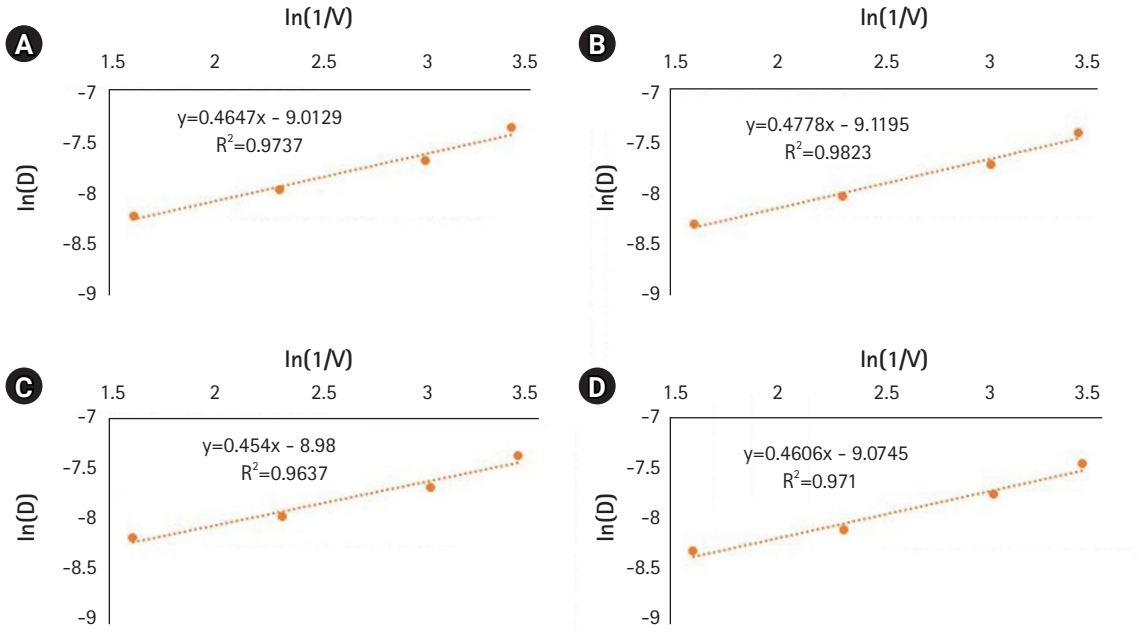


**Fig. 4.** The rate of dose fall-off beyond the target region by plotting ln(1/V) vs. ln(D) in the x and y axes, respectively, for all the cases planned with sequential ncVMAT (A), SIB ncVMAT (B), sequential cVMAT (C), and SIB cVMAT (D). cVMAT, coplanar volumetric-modulated arc therapy; ncVMAT, non-coplanar VMAT; SIB, simultaneous integrated boost.

In our study, the dosimetric advantage in the treatment of head and neck cancer patients was investigated and the robustness in the planning techniques was assessed by comparing ncVMAT and cVMAT in photon therapy. We found that the ncVMAT plan is more robust than the cVMAT plan for both target and normal tissues with increasing target coverage and conformity. Some studies indicate that coplanar beam arrangements in VMAT generate sub-optimal plans [28,29]. Non-coplanar arrangements of the beam with acceptable degrees of freedom generate better plans especially with regards to the OARs compared to coplanar beam arrangements. The improvement in the OAR dose parameters was observed with ncVMAT compared to cVMAT with other studies [30,31].

The delivery efficiency was assessed by choosing dose constraints to OARs and optimization parameters for both types of treatment plans [32]. In the daily treatment scenario for 6–7 weeks, the treatment delivery time is longer for ncVMAT. The benefit in coplanar beam arrangements is that gantry rotates in a smooth trajectory reducing overall treatment time and collision-free degrees of freedom. Furthermore, the range of MUs was larger and so was the IMRT ratio in the ncVMAT than cVMAT because of the complexity of beam optimization creating multiple apertures or segments of small field throughout different couch, collimator and gantry angles [33].

In our study, the same optimization parameter, i.e., number of arcs, gantry start and end angles, couch and collimator angles, number of control points per arc and minimum segment width were used in both of the sequential and SIB techniques for both types of the treatment plan. Therefore in the PTV for phase-I sequential technique, there was a non-significant change in the values of $CI_{RTOG}$, CN, $ID_{95\%}$, DHI, and $HI_{RTOG}$ because of extra degrees of freedom which gives the optimizer additional space to reduce the dose to the OAR without reducing the dose to the target region for a comparably less prescription dose than SIB technique. On the other hand, in the SIB technique, all the dosimetric parameters for evaluation of target except CN in PTV-low showed significantly better results for ncVMAT.

Concerning OARs, for parotid glands, significant sparing was observed on $D_{50\%}$ of the left parotid. The achievable dose in the parotid glands depends on the involvement in the PTV. The achieved $D_{mean}$ of the parotid glands was $>26$ Gy in our study as in certain other studies for the SIB plans [34,35]. For the spinal cord and brainstem, the achieved dose for $D_{max}$ was $<45$ Gy and $<54$ Gy for all the planning techniques and a non-significant dose reduction was observed in the ncVMAT comparably from cVMAT. In brachial plexus, $D_{max}$ should be $<66$ Gy for head and neck cases in terms of plexopathy. In our study, dose constraints for bilateral brachial plexuses were achieved. A significant dose reduction was observed on $D_{max}$ for the right brachial plexus [36-38].

A significant dose reduction was observed for bilateral lung apices in the cVMAT plans. The reason behind the increase in dose in


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bilateral lung apices is the exiting path which was directly through the lung apex regions. $D_{mean}$ for bilateral lung apices was reduced by nearly 2 Gy based on the overall prescription dose in the coplanar beam arrangements.

Irradiation of tumors in the head and neck cancer patients is technically challenging especially in the patients with a short neck or high shoulders. Considering patient comfort, we had fixed the patient position by applying a mask. Higher stage head neck cases required comprehensive irradiation of the neck region extending inferiorly to the level of the lung apices. Owing to the body structure, if we planned with coplanar beam arrangements, dose to the healthy tissue of the shoulder region would be higher than non-coplanar beam arrangements because of the photon path length to the PTV, i.e., photon beams had to pass through the shoulders and soft tissue of neck region [39]. For this reason, we evaluated the dose for bilateral humeral heads. A significant dose reduction was noted for $D_{max}$ of bilateral humeral heads in non-coplanar beam arrangements.

The use of non-coplanar beam arrangements resulted in a broader dose bath because of quantitatively more irradiated volume in the healthy tissue. For that reason, the clinical relevance of the dose bath has to be considered carefully. A significant increase in integral dose in the patient body was observed although the difference was very less. When evaluating the lower dose volume in the healthy body tissues we observed that $V_{5Gy}$ was increased and conversely $V_{10Gy}$ was reduced in ncVMAT.

Due to the contributions of patient and collimator scatter, the energy spectrum is softer outside the treatment field than within the target volume [40,41]. The amount of low dose volume outside the treatment field is high in VMAT plans due to the distance from the field edge to the beam entry point through the body surface. The dose outside the treatment field also depends on the size of the target, increasing with increasing target volume because larger irradiated volumes produce more patient scatter in the body [42]. Gradually decrease in the average volume (V) encompassed by a certain dose (D) was following a logarithmic pattern for an increase in the dose [43-46]. As depicted in Fig. 4, the rate of dose fall-off was higher in the non-coplanar beam arrangement than coplanar because of the high number of degrees of freedom available in the optimization process restricting the dose to the nearby OARs and healthy soft tissues of the patient body. The amount of intensity modulation was higher in the non-coplanar beam arrangements because the optimization was done with different beam angles according to the couch position with gantry-collimator adjustment [47].

In conclusion, VMAT plans with non-coplanar beam arrangements showed significant dosimetric advantages both on target coverage and OAR sparing compared with coplanar beam arrangements in the treatment of head and neck malignancy. However, there was a significant increase in MU, total delivery time, uncertainty in proper patient positioning, integral dose to the patient body, and dose to the bilateral lung apices in the ncVMAT plans. Conversely, there was a significant improvement in plan robustness, target conformity, low dose to the healthy tissues of shoulders and neck region, and both bilateral brachial plexus and humeral heads. One of the late toxicity in head and neck patients with contribution from both, surgery of neck as well as intermediate to low dose deposition by radiation therapy in neck and shoulders, results in fibrosis and reduced range of motion of shoulder joint and neck. The dose reduction to the shoulder joint and lower neck region by ncVMAT may translate in lesser late fibrosis of the same and maybe further studied clinically. The minimally increased dose deposition in ncVMAT to lung apices may not contribute to any increased pulmonary toxicity and may also be clinically confirmed at the same time.

## Conflict of Interest

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

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Case Report

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# Exceptional response to radiotherapy in unresectable pleuropulmonary blastoma of a child

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Pleuropulmonary blastoma (PPB) is a rare intrathoracic neoplasm in children. Although surgery with or without chemotherapy mainly conducted, the response of radiotherapy (RT) has not been evaluated yet. For unresectable tumor, RT might be considered as one option to decrease tumor extent to relieve obstructing symptoms or to facilitate successive treatment. We report one child in whom PPB with DICER1 mutation recurred after surgery and lead to respiratory distress. She emergently received palliative RT with a relatively low dose (20 Gy), and symptoms sufficiently relieved. Even she showed an 84.3% reduction in diameter and maintained the remission status for 1 year. These might reflect possible radiosensitivity of PPB, and further investigations of RT might be necessary for unresectable PPB.

**Keywords:** Child, Radiotherapy, Pleuropulmonary blastoma

## Introduction

Pleuropulmonary blastoma (PPB) is a rare neoplasm that occurs mainly in children and arises from the lung or pleura, with highly aggressive features [1]. Clinically, PPB presents with non-specific symptoms, commonly including respiratory distress, fever, and chest pain. Although there is currently no standard treatment guideline for PPB, mainly surgical resection and chemotherapy, if necessary, are performed [2]. However, the role of radiotherapy (RT) is unclear to date, and while one case report described a response to RT for unresectable PPB in an adult [3], the response and efficacy of RT in treating gross residual PPB has not been reported in pediatric patients who account for approximately 45.5% of patients with PPB [4]. In this report, we present one case showing the exceptional response to short-course RT for respiratory failure due to recurred PPB with DICER1 mutation in a child.

## Case Report

A 6-year-old girl who had received right upper lobectomy for type II PPB in May 2015 presented fever, cough, sputum, and dyspnea from 10 days ago. She was prescribed medicine for upper respiratory infection in another hospital. Symptoms did not improve, and she was referred to the emergency department for right lung total collapse on chest X-ray of another hospital with tachypnea and wheezing on April 26, 2019. Chest computed tomography (CT) found newly noted about 22.3 × 13.2 × 12.7 $cm^3$ sized cystic and solid mass in the right hemithorax (Fig. 1A). After a disease-free interval of 4 years, PPB recurred with rapid progression. In echocardiography on April 27, 2019, both atria collapsed, and compressed superior and inferior vena cava were observed. IVADo regimen (ifosfamide, vincristine, actinomycin D, and doxorubicin) was performed to relieve the vascular obstruction from April 28, 2019.

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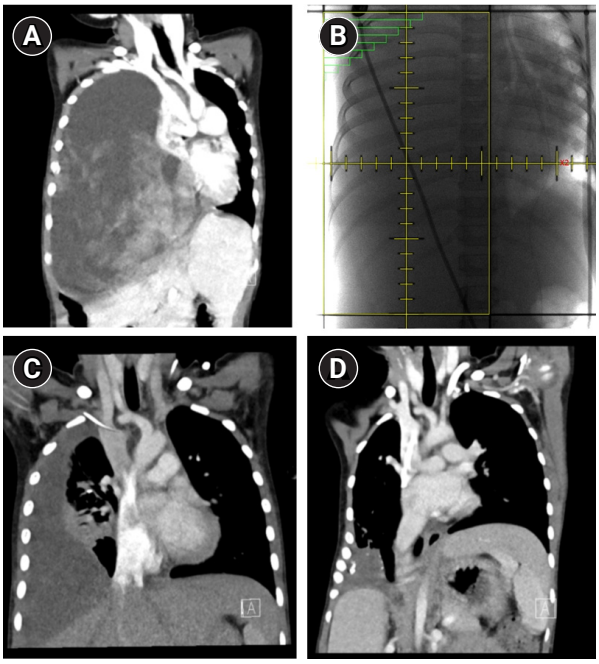


**Fig. 1.**Contrast-enhance chest computed tomography scans: (A) before treatment, (B) radiotherapy field of patient, (C) 1 month after radiotherapy, and (D) at last follow-up.

However, 2 days after chemotherapy, she was transferred to a pediatric intensive care unit for applying mechanical ventilator due to respiratory failure and obstructive shock with tumor progression. For respiratory symptom relief, emergency RT was delivered from April 30 to May 3, 2019. RT to right lung mass was given with anteroposterior/posteroanterior field (11 × 20 $cm^2$) weighted 1:1 to a total dose of 20 Gy in 4 fractions using 10 MV photon (Fig. 1B). Echocardiography on May 8, 2019 found no more compression of right atrium and superior vena cava. One week after RT, extubation was done and no oxygen desaturation observed. However, because she presented dyspnea, oxygen was supplied via nasal prong (up to 4 L/min) or facial mask (up to 7 L/min). Ten days later, her blood-oxygen saturation level ($SpO_2$) was 97% in room-air and nasal prong was used intermittently. After one month without any further chemo- or radiotherapy, the cystic and solid mass in the right hemithorax markedly reduced to 6.5 × 6.2 × 5.3 $cm^3$ in chest CT (Fig. 1C). She had remained in stable respiratory status in room-air and could re-started 4 cycles of IVADo. PPB continued to decrease and was measured up to 3.5 × 3.1 × 2.5 $cm^3$ in the last follow-up chest CT (9 months after RT) (Fig. 1D). From December 2019, pulse VAC (vincristine, actinomycin D, and cyclophosphamide) treatment started. After 4 cycles of chemotherapy, needle biopsy of residual tumor on March 31, 2020 found no tumor, only fibrous tissues. In this patient, next-generation sequencing analysis using a previous surgical sample detected DICER1 mutation (c.5125G>A).

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-1907-118-1048). Because of the retrospective review of the case and excluding all patient identifiers in manuscript and figures, the requirement for obtaining informed consent of patient in this report was waived.

## Discussion

PPB is an extremely rare and distinct primary malignant neoplasm of lung and pleura, accounting for 0.5% of all malignant neoplasms in the pediatric population [5,6]. In the early stage of tumorigenesis, the epithelium of airspace expands and forms the cyst. Mesenchymal cells undergoing malignant transformation show sarcomatous overgrowth, finally producing solid masses [7]. Depending on where neoplasm is in the tumorigenesis stage, PPB is divided into three subtypes based on its morphological features [5]. Type I is purely cystic with subtle malignant transformation, typically occurring in very young children under about 2 years old. If type I PPB has no primitive cell component, it is designated as type Ir (the "r" means regression or non-progression) [8]. Type I could progress to type II or III, but not all. Hill et al. [7] reported that among 51 patients with type I PPB, 5 patients experienced local recurrence or disease progression. Of 4 patients with available microscopic sections of the recurred PPB, 2 progressed to type II, and the others showed type III pattern. Type II and type III exhibit similar solid components, and type II PPB has residual cystic areas. In type II and type III, relapse at the central nervous system with or without local recurrence is the major failure pattern (59.1%) [8]. The 5-year overall survival rate for type I, II, and III was 89%–100%, 67%–71%, and 53%–67%, respectively [2,9]. This result emphasizes that type I PPB should be prevented from progressing to type II and III.

Currently, there is no standard treatment, but the International Pleuropulmonary Blastoma Registry recommends general treatment options. The treatment of choice for patients with type I and Ir PPB is complete surgical resection. In these patients, adjuvant chemotherapy does not affect the progression of the disease and patient survival. For patients with type II and III PPB, a multimodal approach is recommended, including chemotherapeutic regimens for rhabdomyosarcoma before or after surgery [2]. In terms of RT, previous reports did not show a survival benefit [8,10]. However, although experience with one patient with recurrent PPB is inconclusive, even low dose short-course RT consisting of 20 Gy could rapidly reduce the size of PPB in emergencies such as respiratory failure. Accumulation of clinical experiences about the use of RT is needed.

DICER1 gene has a critical regulatory role in the generation of microRNA [11]. Moreover, DICER1 has been known to play an es-

sential role in lung morphogenesis [12]. Messinger et al. [8] found that 66% of patients with PPB possessed a heterozygous, deleterious mutation of DICER1. There were no differences in both clinical features and prognosis between patients harboring a DICER1 mutation and those not. In that report, only 20% of patients (n = 47) with type II and III PPB were treated with RT, and the prognostic significance for a DICER1 mutation in patients receiving RT was not analyzed.

Several in vitro experiments have reported that DICER is associated with DNA damage response (DDR) [13-15]. DNA damage response RNAs are generated by DICER and DROSHA [13], and these recruit DDR factors to the DNA lesions [14]. It has also been demonstrated that the depletion of DICER1 results in endogenous DNA damage and delay of DDR [15]. Considering that RT causes tumor cell death by DNA damage, DICER1 mutation of PPB might be closely related to increased radiosensitivity. Comprehensive biologic researches on radiosensitivity and DICER1 would be required. Furthermore, because most patients with PPB have DICER1 mutation, it could be expected as a target gene of RT.

In conclusion, PPB is an aggressive intrathoracic neoplasm with poor prognosis in early childhood. Multimodality approaches to treat PPB, including surgery, chemotherapy, and RT, should be considered. Our experience suggests that PPB might have high radiosensitivity.

## Conflict of Interest

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

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