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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The inflammatory musculoskeletal conditions are a large group of disorders composed mainly of arthritis. The term arthritis in itself does not refer to a single disease condition, similarly the types of arthritis such as osteoarthritis (OA) have various subtypes.

In 2017, the Centers for Disease Control and Prevention (CDC) reported the prevalence of arthritis in the United States was 23% with over 54 million people having the disease. In addition, over 60% of the people in the United States with arthritis are in the working age group (18–64 years) [1].

Inflammmatory musculoskeletal conditions are a common group of diseases among the elderly, worldwide. They are characterized by articular degenerative changes accompanied with often debilitating pain. Treatments often involve life-long analgesic therapy or joint replacement in extreme cases. The aim of this current review is to look at the role of radiation treatment with the hope of further study into the effectiveness of radiation treatment in reducing pain, eliminate or reduce the need for life-long analgesic therapy and thereby avoiding the analgesics’ side effects. Extensive literature search was done on PubMed and other available data base and the findings are presented and discussed.

Inflammmatory musculoskeletal conditions are a common group of diseases among the elderly, worldwide. They are characterized by articular degenerative changes accompanied with often debilitating pain. Treatments often involve life-long analgesic therapy or joint replacement in extreme cases. The aim of this current review is to look at the role of radiation treatment with the hope of further study into the effectiveness of radiation treatment in reducing pain, eliminate or reduce the need for life-long analgesic therapy and thereby avoiding the analgesics’ side effects. Extensive literature search was done on PubMed and other available data base and the findings are presented and discussed. Literature showed that many countries in Europe, especially Germany use radiation routinely for the treatment of many degenerative disorders including osteoarthritis with good results and few side effects. A pilot study is therefore recommended with a view to establish the effectiveness or otherwise of this treatment method in patients.

**Keywords:** Osteoarthritis, Joint diseases, Radiotherapy dosage, Radiobiology

**Introduction**

The inflammatory musculoskeletal conditions are a large group of disorders composed mainly of arthritis. The term arthritis in itself does not refer to a single disease condition, similarly the types of arthritis such as osteoarthritis (OA) have various subtypes.

In 2017, the Centers for Disease Control and Prevention (CDC) reported the prevalence of arthritis in the United States was 23% with over 54 million people having the disease. In addition, over 60% of the people in the United States with arthritis are in the working age group (18–64 years) [1]. In Canada, arthritis is the 2nd and 3rd most common condition in women and men respectively, affecting over 4.2 million people which accounts for 16% of the population 15 years and older [2]. Similar to the data form the United States, arthritis also significantly affects the working age group in Canada with nearly 3 in 5 people with arthritis in the country aged between 15 and 64 years [2].

Disabilities as a result of musculoskeletal disorders increased by 45% from 1990 to 2010. Furthermore, OA is listed by the World Health Organization as the fastest increasing major health condition and ranked as the 2nd leading cause of disability [3]. OA is the underlying cause for more than 90% of the increasing number of total hip or knee joint replacement operations worldwide [4].

Studies from Africa show the prevalence of OA in South Africa is over 29.5% while that of Nigeria is 0.4% [5]. The Community Oriented Program for Control of Rheumatic Diseases (COPCORD) studies in Asia show the prevalence of OA is as high as 34% among people in the 60–64 years age bracket [6]. In the United States, the prevalence of OA increased from 6.6% in 1999 to 14.3% in 2014 [7]. However, in the same time-period, in the United States, the prevalence of rheumatoid arthritis (RA) reduced from 5.9% to 3.8% [7].

Rheumatoid arthritis is the 2nd highest attributable disease to global disability [8]. It has a two-fold morbidity among women compared to men [9]. And it has been estimated that China had...
over 5 million people diagnosed with rheumatoid arthritis by 2013 [10]. In Northern Europe and North America, the prevalence of RA is estimated to be 0.5%–1% [11–14]. The prevalence of RA in the Middle East and North Africa region is among the lowest at 0.16% [9], while in South Africa it is 2.54% [5].

Ionizing radiation has been employed in treating malignant disease conditions for the last few decades with great success and outstanding improvement in the overall outcome of cancer care. Ionizing radiation has also been employed for the treatment of some benign conditions including keloids, recurrent pleomorphic adenoma, Graves’ orbitopathy, giant cell tumors of the bone, aneurysmal bone cysts and benign CNS tumors [15]. However, the role of radiation in the treatment of benign tumors is not as pronounced and well established as in its use for malignant conditions.

There is worldwide acceptance of the use of ionizing radiation in managing the aforementioned benign disease conditions. However, ionizing radiation is not a widely used treatment option in managing painful inflammatory/degenerative skeletal disease conditions [16]. The only part of the world where this is routinely done is in Central Europe, particularly Germany, Austria and Switzerland, and to a lesser degree in some parts of Eastern Europe [17].

Historically, there have been accounts of treating arthroses and arthritis with ionizing radiation. As early as 1952, Hill and Windeyer [18] reported on the utility of X-ray irradiation in treating OA and ankylosing spondylitis. In the same article they mentioned the fact that the earliest published report on the benefit of ionizing radiation in cases of people suffering from joint diseases was by Sokoloff in 1897. In addition, Hall and Windeyer [18] also mentioned the fact that Anders et al. [19] in 1906 were the first to use the analgesic effects of X-rays to treat arthritis.

After the 1950’s, radiation therapy for these conditions went into the history books for fear of secondary malignancies coupled with a lack of understanding of the mechanisms involved in radiation treatment for benign conditions [17,20,21]. However, over the years, the fields of radiobiology and radiation physics have evolved and improved. Therefore, it is becoming apparent that the use of radiation therapy in treating inflammatory/degenerative skeletal conditions was prematurely abandoned. This may have been due to poor understanding of the effects and mechanisms of the therapy. Muscoplat et al. [20] in their letter to the editor of the International Journal Of Radiation Oncology, Biology and Physics on radiation therapy for inflammatory arthritis concluded “There is a disconnect in medicine, whereby new therapies are enthusiastically adopted (e.g., biologic therapy for ankylosing spondylitis), even if risky, whereas old therapies, once abandoned, are overlooked even if the therapy was effective and the technology has been extensively improved (e.g., megavoltage radiation therapy). Radiation therapy is an “old therapy”; old therapies traditionally do not get studied by “modern” clinicians. In this instance, we may be missing an important and useful treatment. We would welcome a discussion of these topics to shed further light on mechanisms of disease, risk of therapies (and especially radiation therapy), and potential clinical studies that may help revive (if appropriate) an “old therapy” for patients with resistant spondyloarthropathy” [20].

The successful accounts of and extensive use of radiation for benign conditions in countries like Germany serve as reason to take a second look into this treatment modality, especially in low and middle income countries (LMICs) where the one-off cost model that may emerge may provide an incentive as opposed to the lifelong medication that arthritis often requires. It is noted that 8%–10% of radiotherapy procedures in Germany are for benign disorders, and 70% of these indications are for painful disorders of the locomotor system [22]. Over 9,000 patients with OA are treated with low dose radiotherapy every year, in order to relieve pain [23].

**Radiobiology**

The mechanisms by which ionizing radiation result in a therapeutic effect in benign diseases have been hypothetically classified as can be found in the review article by Trott and Kamprad [21]. These are as follows:

1. **Anti-proliferative radiation effects:** This is responsible for the utility of radiotherapy in treating keloids, Dupuytren’s contractures, fibromas or prevention of heterotopic ossification. Doses are generally 10 Gy or higher.

2. **Immunomodulatory radiation effects:** This is responsible for the local suppression of autoimmune disorders such as endocrine orbitopathy. Optimal doses are also greater than 10 Gy.

3. **Anti-inflammatory radiation effects:** This is responsible for the analgesic effect of radiotherapy in inflammatory musculoskeletal conditions such as osteoarthritis, ankylosing spondylitis, periartitis humeroscapularis or epicondyritis humeri. Total doses of 2–6 Gy are given in fractions of 0.5 Gy (though there are clinical evidences proving 1 Gy per fraction is as efficacious) [16,24,25].

4. **Functional radiation effects:** An ill-defined group assumed to effect through modulating responses of the autonomic nervous system or by interfering with gene activation. Optimal doses are usually less than 2 Gy.

The cellular effects of radiation applicable in treatment of degenerative/inflammatory skeletal disorders have been noted by in vitro models and animal studies. They include:

1. **Modulation of endothelial cells:** Endothelial cells play a large role in inflammation. Once activated, they secrete cytokines and
Recruit inflammatory leucocyte and also allow transendothelial migration of leucocytes. In vitro and in vivo studies have proven an increase in the expression of intercellular adhesion molecule 1 (ICAM-1) in endothelial cells upon exposure to ionizing radiation doses. This is noted to be linearly dose-dependent and peaking at doses between 4–10 Gy [21]. In addition, E-selectin—endothelial-leukocyte adhesion molecule 1 (ELAM-1)—secretion by endothelial cells is even more radiosensitive, with its messenger ribonucleic acid (mRNA) expression increasing within 2 hours of exposure to doses as low as 0.5 Gy. However, this involves activation by nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [21]. On the other hand, for benign diseases, endothelial cells existing in inflammatory condition are in a different cellular condition and thus respond differently. Experiments have demonstrated a reduced adhesion of leucocytes onto activated endothelial cells upon irradiation of low doses between 0.3–1 Gy [21,26]. This might be through the reduction in E-selectin expression in endothelial cells noted by Maggiorella (as cited in Trott and Kamprad [21]), upon exposure to low dose radiotherapy [21]. In addition, these effects have been observed to functionally coincide with nonlinear expression of the anti-inflammatory cytokine transforming growth factor β (TGF-β) [27–29].

(2) Modulation of leucocytes: Irradiation of peripheral blood mononuclear cells (PBMC) and polymorphonuclear cells (PMNC) result in a discontinuous increase in apoptosis which reaches its peak at doses of 0.3–0.7 Gy. This coupled with enhanced proteolytic cleavage of L-selectin on apoptotic PBMC and the effect of low dose radiation (LDRT) on endothelial cells stated above reduces the number and recruitment of inflammatory cells. Furthermore, PMNC irradiated with doses below 1 Gy have been noted to have reduced secretion of chemotactic cytokine chemokine ligand 20 (CCL20) and modulated mitogen-activated protein (MAP) kinases and protein kinase B [27–29]. In addition, following LDRT of activated macrophages there is reduced expression of inducible nitric oxide (NO) synthase which is responsible for the synthesizing of NO. There is also reduced release of reactive oxygen species and reduced production of superoxide, reduced secretion of pro-inflammatory cytokine interleukin 1 and increased secretion of TGF-β1 by pre stimulated macrophages [27,30]. These effects all contribute to an anti-inflammatory cytokine microenvironment for macrophages [27].

Calabrese et al. [31] in their study determining the optimal dose for radiotherapy of human inflammatory disease conditions noted that ionizing radiation elicits a pleiotropic effect in macrophages with two distinct phenotypes upon radiation depending on the dose. A pro-oxidative M1 phenotype results with X-rays of dose in the range used for treating malignancies. However, macrophages exposed to low dose radiotherapy with dose per fraction <1 Gy are polarized to the M2 phenotype which are anti-inflammatory.

### Animal Models

These anti-inflammatory effects of LDRT were also corroborated by in vivo studies. Von Pannewitz [32] as reported in the review article by Arenas et al. [29] noted an improvement of clinical symptoms and reduction of synovial fluid and proliferation of synovial cells in rabbits knee arthritis once irradiated with 1 Gy of ionizing radiation. Similarly, another model using rats knee arthritis noted significantly reduced bone loss, cartilage degradation and joint swelling when irradiated with 4 Gy in 4 daily fractions of 1 Gy compared to significantly increased bone loss when exposed to 5 Gy single fraction of irradiation [33]. A few animal studies also had histological evaluation done on the animals after exposure to low dose radiotherapy and they showed reduced histological evidence of inflammation [34–36]. Hildebrandt et al. [37] induced adjuvant arthritis in rats to model rheumatoid arthritis by intradermally injecting heat inactivated Mycobacterium tuberculosis in paraffin oil into the base of the tail of rats. The study revealed LDRT (5 Gy in 5 fractions and 2.5 Gy in 5 fractions) resulted in statistically reduced arthritis score and hind paw volume. However, the histopathology revealed a significantly reduced joint destruction but non-significant change in inflammatory infiltrate of the hind paw. A review of animal studies [21] indicate LDRT to be more pronounced in degenerative arthritis than rheumatoid arthritis.

### Indication/Results and Outcomes

There are contemporary reports of LDRT of benign inflammatory/degenerative skeletal conditions (Table 1). Hautmann et al. [24] reported on their prospective trial in which 20 osteoarthritic knees associated with Baker’s cyst were irradiated. They noted LDRT (3 Gy in 6 fractions at 0.5 Gy per fraction or 6 Gy in 6 fractions at 1 Gy per fraction or a single dose of 1 Gy) improved (pain) numeric rating score (NRS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the objective parts of the Knees Society Score significantly at short-term follow-up (6–12 weeks post-treatment) compared to baseline values. The volume of the Bakers cyst also reduced significantly (p = 0.002) at short-term follow-up compared to baseline volume. In addition, there was a persistence in the significant effect of LDRT pertaining to NRS, Knee Society Score, WOMAC score and cyst volume at longer term follow-up (9–12 months).

In another study on a subtype of OA, thumb carpometacarpal osteoarthritis (rhizarthrosis), Kaltenborn et al. [38] analyzed 84 pa-
patients with 101 joints. The patients were treated with 6 Gy in 6 fractions at 1 Gy per fraction over 3 weeks using a 6-MV linear accelerator (LINAC). Multivariate logistic regression indicated remission induction was significantly associated with a larger field size (larger than 6 cm × 4 cm), and negatively associated with initial pain increase during radiotherapy [38].

The meta-analysis by Minten et al. [16] indicated there was insufficient evidence for a positive effect of LDRT in treating OA but, this was due to the absence of high-quality studies. However, their conclusion from the articles they studied was that LDRT decreased pain in 13%–90% of patients in the short term, while a long-term analgesic effect was observed in 44%–87% of patients. The meta-analysis also concluded that 29%–80% of the patients functioning improved on LDRT. However, no study with sufficient quality was retrieved. The authors thus advised a well-designed sham-controlled blinded randomized trial using validated outcome measures.

In a study on a total of 141 patients treated from 1983–2004 with LDRT (83% received 6 Gy in 6 fractions at 1 Gy per fractions, the others received a total of 4–6 Gy) for periartitis of the shoulder by Niewald et al. [17], 56% of patients reported pain relief and improvement of mobility. On follow-up assessments at a median of 4.5 months, 69% of the patients reported pain relief, while 89% of patients reported improvement of motility. At a median of 3.9 years post-treatment 73% of patients reported both pain relief and motility improvement. The only side effect noted in one patient was a mild redness of the skin after radiotherapy. There were 7 patients who had swelling to start with. Three of these patients noticed an improvement immediately after radiotherapy, while 5 patients noticed this improvement at a median of 4.5 months thereafter [17].

In a prospective study by Micke et al. [22], 703 patients were treated for calcaneodynia, achillodynia, painful gonarthrosis, bursitis trochanterica, and painful shoulder syndrome with LDRT (6 Gy in 0.5–1 Gy per fractions). Baseline pain as assessed by visual analogue score (VAS) and pain relief according to the four scale “Von Pannewitz” (VPS) [32] were determined. These were also assessed immediately post LDRT. They also assessed the long-term effect of the treatment by systemic telephone survey in which the VPS was used to know which patients had a good long-term response. Their results showed that the median VAS scores immediately after treatment compared to before treatment was significantly lower in all categories of diseases and in all the patients (p < 0.001). Comparing the proportion of patients tagged as good response by VPS on completion of LDRT to those with good response on long-term follow-up indicated all disease categories except for those with painful gonarthrosis had a higher proportion with good response to treatment on long-term follow-up compared to immediately after completing radiotherapy. The authors concluded the enthesopathies were more likely to achieve complete remissions with LDRT compared to gonarthrosis because gonarthrosis are due to pathologically irreversible processes in which bony and cartilaginous destructions occur. These cannot be reversed by radiotherapy. However, LDRT can still be of utility in relieving the accompanying inflammation and pain in the acute setting. And no side effects were observed [22,25,32].

Literature [39] indicates a lack of efficacy in the use of ionizing radiation for treating rheumatoid arthritis. The authors conducted a randomized, controlled, double blind study in which one of the patients’ joints was treated with X-rays from a LINAC (20 Gy in 10 fractions over 2 weeks) and another joint was treated by sham radiation. There was no significant change noted in the scores for tenderness, swelling, pain or disease activity and the study was stopped for ethical reasons. However, with regard to the radiobiology of X irradiation of benign inflammatory/degenerative musculoskeletal condition, the dose irradiated in this study was too high. This might be the reason why no effect was observed. Notwithstanding, as was earlier noted the anti-inflammatory effect of LDRT on rheumatoid arthritis is not as pronounced as on degenerative arthritis [21]. The forms of radiation therapy applicable in rheumatoid arthritis include radiation synovectomy through intra-articular injection of a radionuclide [40] or total lymphoid irradiation [41].

Radiotherapy Planning

Megavoltage or orthovoltage radiotherapy machines may be utilized. The German Society for Radiooncology (Deutsche Gesellschaft für Radioonkologie [DEGRO]) recommends the target volumes for enthesopathies should encompass the complete involved insertion area including the nearby bony and muscular tissues. For painful arthroses, DEGRO recommends target volumes must include the articular cartilage, the nearby bony structures, the entire synovia, the surrounding muscles, and the periarticular connective tissues [25].

Appropriate fields to cover the target volume and provide a uniform dose distribution should be used. Large joints such as the shoulder and knee are treated with two opposed (anteroposterior/posteroanterior) fields. While smaller joints of the hand can be treated with a single (direct) field [25].

In situations where the pain persists or the pain relief is insufficient 6–12 weeks post radiotherapy, a second series may be recommended [25,42,43].

Radiation Risk

1. Non–carcinogenic effect

There are hardly any early or late effects of radiotherapy from LDRT.
In the study by Niewald et al. [17], the only side effect was a mild redness of skin after radiotherapy (acute dermatitis) in one patient. There are no accounts of relevant side effects due to anti-inflammatory radiotherapy to the knee in published literature [24]. In the study by Micke et al. [22] none of the 437 patients followed up for a median of 33 months developed any early or late effects.

2. Radiation carcinogenesis

It is established that X-ray irradiation has the potential to result in secondary cancers or radiation induced cancer. These secondary cancers include soft tissue sarcomas (usually malignant fibrous histiocytoma [MFH] and fibrosarcoma), thyroid cancer, colon cancer and leukemias [31,44,45]. This, in addition to accounts of radiation induced malignancies from survivors of the atomic bombs in Japan and other nuclear accidents, is what led to the worldwide decline in the use of radiotherapy as an option for the treatment of inflammatory/degenerative musculoskeletal conditions [17,31]. The first criteria for radiation induced sarcoma were established by Cahen et al. [46]. They include: (1) the sarcoma developed within the field or path of the radiation beam; (2) a 5-year latency period between the exposure to radiotherapy and the clinical appearance of the sarcoma; and (3) histologically confirmed diagnosis of the sarcoma. Arlen et al. [47] later modified the criteria to include the tissues adjacent to the path of the radiation beam also at risk for development of a sarcoma; and the latency period was reduced to 3–4 years. Studies have shown that post-radiation sarcomas occur post exposure to a median dose of about 50 Gy (ranging from 8 Gy to over 60 Gy) and a median latency period of 10 years (ranging from 2 years to up to 50 years) [48]. An estimate of 0.03% of patients who receive radiation to 0.2% of patients who have received radiation and survived 5 years later develop post-radiation sarcoma [48]. A study by Kuttesch et al. [49] noted no post-radiation sarcoma in patients receiving less than 48 Gy compared to an absolute risk of 0.03% of patients who have received radiation to 0.2% of patients who have received radiation [48]. An estimate of 0.03% of patients who receive radiation to 0.2% of patients who have received radiation and survived 5 years later develop post-radiation sarcoma [48]. A study by Kuttesch et al. [49] noted no post-radiation sarcoma in patients receiving less than 48 Gy compared to an absolute risk of 0.03% of patients who have received radiation to 0.2% of patients who have received radiation [48].

As early as 1990, a case report of a patient who was treated for ankylosing spondylitis at the age of 21 (1947/8) was published. He received a skin dose of 20 Gy in 10 fractions to the entire length of the vertebral column using a 200-kVp X-ray machine. In 1987, as a 61-year-old male patient, he presented with a history of upper thoracic pain which had been on for several years and a subcutaneous non-tender lesion at the upper thoracic paravertebral region. Histopathology of the resected tumor was revealed to be a leiomyosarcoma. However, this patient received 20 Gy of radiation therapy X-ray photons, far above the upper limit of the total dose to be received in LDRT (6 Gy) [44]. The authors also noted that, upon exposure to therapeutic single dose of ionizing radiation, an increase in death rate from cancers was noted. However, this increase did not reach statistical significance. In addition, excluding leukemia and colon cancers, the increased death rate peaked at 10–12 years post radiation exposure with peak persistence till 25 years [44].

LDRT for benign conditions including inflammatory/degenerative musculoskeletal conditions has been utilized in Germany since before the 1990’s. And since then there has been considerable discussion and research into the risk of secondary cancers [31]. Radiation risks associated with LDRT are examples of stochastic effects. Stochastic effects are random statistical occurrences, the severity of the effect is not dependent on the dose of ionizing radiation, only the probability of the effect occurring is dose dependent, probably with no threshold [52]. To assess radiation risk, genetic and cancer risks need to be assessed. One needs to calculate the effective dose of radiation to estimate cancer risk. To do this coefficients and values published by the International Commission on Radiological Protection (ICRP) on the results of a reassessment of radiation risk they undertook in 2007 are used [27].

The effective dose estimates the tissue weighted sum of the equivalent doses in all specified tissues and organs of the body and is defined by the formula below:

$$E = \sum T W_T H_T = \sum T W_T \sum R W_R D_{R,T}$$

where $E$ is the effective dose, $T$ is the tissue or organ of interest, $W_T$ is the tissue weighting factor (Table 2), $H_T$ is the equivalent dose absorbed by tissue $T$, $R$ is the radiation type, $W_R$ is the radiation weighting factor, $D_{R,T}$ is the mass-averaged absorbed dose in tissue $T$ by radiation type $R$ [27].

The unit of effective dose is Sievert. Each type of ionizing radiation has a weighting factor, for photons for example, the $W_e$ = 1. Each organ has its $W_T$, which further modifies the effective dose (Table 2). Each nation’s nuclear regulatory agency factors in $W_T$ to arrive at national radiation protection policies and regulations [27].

3. Genetic risk estimate

The ICRP in 1991 estimated the probability of severe genetic damage in future generations to be 1%/Sv. The first and second generations risk are estimated at 0.15%/Sv, while the risk of the third and subsequent generations is 0.7%/Sv [27,53]. However, the 2007 estimates for genetic risks are much lower [27,54].
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design (sample size)</th>
<th>Disease condition</th>
<th>Target site(s)</th>
<th>Dose per fraction/total dose</th>
<th>Results</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niewald et al.</td>
<td>Retrospective observational (n = 141)</td>
<td>Periarthritis</td>
<td>Shoulder</td>
<td>1 Gy/6 Gy</td>
<td>Cobalt 60, 4 MV and 6 MV LINAC, electrons, orthovoltage</td>
<td>• Outcome: % Pannewitz class</td>
</tr>
<tr>
<td>Micke et al.</td>
<td>Prospective observational (n = 703)</td>
<td>Calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome</td>
<td>Various</td>
<td>0.5 Gy/6 Gy or 1 Gy/6 Gy</td>
<td>LINAC and orthovoltage</td>
<td>• Outcome: VAS and VPS</td>
</tr>
<tr>
<td>Hautmann et al.</td>
<td>Prospective observational (n = 20)</td>
<td>Baker's cyst</td>
<td>Knee</td>
<td>0.5 Gy /3 Gy or 1 Gy/6 Gy</td>
<td>6 MV or 15 MV LINAC</td>
<td>• Outcome: NRS, KSS, cyst volume</td>
</tr>
<tr>
<td>Kaltenborn et al.</td>
<td>Retrospective observational (n = 84)</td>
<td>Osteoarthritis</td>
<td>Thumb (carpometacarpal joint)</td>
<td>1 Gy/6 Gy 6 MV LINAC</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

(Continued to next page)
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design (sample size)</th>
<th>Disease condition</th>
<th>Target site(s)</th>
<th>Dose per fraction/total dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graninger et al. [39]</td>
<td>Randomised controlled double blind study (n = 6)</td>
<td>Rheumatoid arthritis</td>
<td>Varying joints</td>
<td>2 Gy/20 Gy 20 MeV LINAC</td>
<td>Outcome: joint tenderness and swelling expressed on a 0 to 3 ordinal scale. No therapeutic effect noted when irradiation was compared to sham (placebo).</td>
</tr>
<tr>
<td>Ott et al. [43]</td>
<td>Prospective randomized trial (n = 199)</td>
<td>Benign painful elbow syndrome</td>
<td>Elbow</td>
<td>0.5 Gy/3 Gy or 1 Gy/6 Gy orthovoltage</td>
<td>Outcome: VAS and comprehensive pain score No side effects observed. Overall response rate directly after radiotherapy –80%, 6 weeks after –91%, 3 years after –94%. No significant difference in outcomes between the 0.5 Gy and 1 Gy per fraction regimens.</td>
</tr>
<tr>
<td>Gross et al. [64]</td>
<td>Prospective randomized study (n = 30; 14 RT vs. 16 ESWT)</td>
<td>Supraspinatus tendon syndrome</td>
<td>Shoulder</td>
<td>RT: 0.5 Gy/3 Gy Cobalt-60 vs. ESWT 2000 pulse 3X at 1-week interval</td>
<td>Outcome: Age corrected constant score and side effects were compared between RT and ESWT. In average RT group age corrected constant score improved from 47.6 points before treatment through 79.5 points after 12 weeks to 87.4 points after 52 weeks. In ESWT average age corrected constant score improved from 50.1 points before treatment through 91.4 points after 12 weeks to 97.8 points after 52 weeks. No acute side effects due to RT were observed. One patient had pain and one had moderate skin irritation after ESWT.</td>
</tr>
<tr>
<td>Keinert et al. [66]</td>
<td>Retrospective observational; no control group (n = 290)</td>
<td>Osteoarthritis</td>
<td>Knee</td>
<td>0.5 Gy/3–4 Gy or 1 Gy/6–8 Gy</td>
<td>Outcome: pain 64% were free of pain or had improved pain immediately after treatment, and 81% 6 weeks after treatment.</td>
</tr>
<tr>
<td>Keller et al. [67]</td>
<td>Retrospective observational; no control group (n = 1,037)</td>
<td>Osteoarthritis</td>
<td>Knee</td>
<td>0.5–1 Gy/4–6 Gy</td>
<td>Outcome: pain Immediately or up to 2 months post treatment 79.3% of patients experienced a slight, marked or complete pain relief. 2–14 years after therapy, 49.1 still experienced a slight, marked or complete pain relief.</td>
</tr>
</tbody>
</table>

VAS, visual analogue score; VPS, four-scale pain score according to von Pannewitz; RT, radiotherapy; LINAC, linear accelerator; NRS, numeric rating score; KSS, Knee Society Score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; ESWT, extracorporeal shock wave therapy.

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4. Cancer risk estimate

It is established that ionizing radiation exposure can result in secondary malignancy. However, the controversy is in the mathematical models to estimate this risk. The ICRP estimates the incidence of cancer from exposure to ionizing radiation to be 5.5%/Sv [54].

The ICRP’s model for radiation safety utilizes the effective dose, doses and dose rate effectiveness factor (DDREF) which obtains a value of 2 in doses utilized in LDRT, and the proportion of the irradiated region to the total body weight [27]. From this a middle-aged man irradiated with 6 Gy in 6 fractions at 1 Gy per fraction to the knee is estimated to have received an effective dose of 0.038 Sv (38 mSv) [54]. The effective dose of a computed tomography (CT) scan to the abdomen ranges up to 20 mSv [27]. Going by the ICRP estimate, this irradiation thus increases the lifetime cancer risk by about 0.038 Sv × 5.5 Sv⁻¹ = 0.2% [27].

In spite of this low risk as estimated by the ICRP, certain researchers, groups and bodies claim the ICRP’s model, which is mainly for whole body exposures to members of the public and occupational exposures, overestimates the true risk of radiation induced cancer for therapeutic radiation.

According to Trott and Kamprad [21], the effective dose method employed by the ICRP to estimate the risk of ionizing radiation exposure to the general population was not adequate when applied to estimating the risk of therapeutic radiation for benign or malignant conditions [55]. This is based on the fact that the types of cancer induced by therapeutic radiation differ from those induced by low dose total body irradiation to the population as in the case of Japanese atomic bombs survivors [31]. They also claim that radiotherapy induced malignancies do not follow the same linear non-threshold (LNT) model used in radiation protection risk assessment. They further state that the LNT model overestimates the true risk of therapeutic radiation induced cancer by one order of magnitude. In addition, these researchers note that the risk of cancer induction from LDRT should rather be based on epidemiologic data of patients who have received such treatment in the past [31].

According to Ottolenghi et al. [56], the most significant factor regarding cancer risk is the anatomical site of treatment. They noted that treatment of conditions in the appendages of the human body such as Dupuytren’s contracture, tennis elbow or heel spur result in a very low cancer risk estimated to be similar to that due to a common diagnostic radiologic procedure. However, the major risk in radiotherapy for benign conditions involving the axial skeleton, which has significant amount of red bone marrow, is leukemia. As such the treatment of these locations should take account of and reduce the mean bone marrow dose [56]. In spite of this leukemia risk, a paper by Cuttler [57] suggests a relatively high threshold dose of 500 mSv for ionizing radiation induced leukemia in humans. Sautter-Bihl et al. [58] used the LNT model to provide a quantitative estimate of cancer risk based on LDRT for treatment of inflammatory joint conditions. To arrive at their estimation, they accounted for factors such as the expected average exposures (assumed to be 6 Gy in 6 fractions at 1 dose per fraction) and differential distance to irradiated areas. They also extrapolated the dose to a whole body dose using an established whole body conversion formula. They thus estimated LDRT for benign inflammatory musculoskeletal conditions to result in additional 20–40 malignancies per million people over a lifetime. They went further to note that the average age of patients receiving LDRT for inflammatory joint disorders was 54 years. They thus argued that the cancer risk for this procedure is of no practical relevance.

In another study into radiation carcinogenesis, a mathematical model estimated at total dose of 6 Gy for OA of the knee relates to an effective dose of 13 mSv, which compares to the effective doses from an abdominopelvic CT scan [59]. The authors of the study further estimated the average attributable life time risk for an induced fatal tumor to be about 0.7 in a thousand patients treated at the age of 50 years. However, the risk further reduces to 0.3 in a thousand patients once treated at the age of 70 years [60].

It should be noted that in less peripheral lesions the risk of radiation induced cancers increases. This is due to the exposure to more sensitive organs such as the red bone marrow and the gastrointestinal tract [16].

### Table 2. Tissue weighting factors according to ICRP 103 (ICRP 2007)

<table>
<thead>
<tr>
<th>Tissue (T)</th>
<th>Tissue weighting factor (WT)</th>
<th>( \Sigma W_T )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow (red), colon, lung, stomach, breast</td>
<td>0.12</td>
<td>0.72</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Bladder, esophagus, liver, thyroid</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>Bone surface, brain, salivary glands, skin</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Remaining tissues ( n = 13 )</td>
<td>0.0092</td>
<td>0.12</td>
</tr>
<tr>
<td>Total</td>
<td>-</td>
<td>1.00</td>
</tr>
</tbody>
</table>

ICRP, International Commission on Radiological Protection.

Remaining tissues: adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (male), small intestine, spleen, thymus, uterus/cervix (female).
In Germany, in spite of these known low estimates of radiation induced cancer, there are established protocols to further reduce the risk. LDRT for inflammatory/degenerative musculoskeletal disorders is only done when standard non-radiation treatments have failed. In addition, patients under the age of 40 years are only treated in exceptional circumstances and even then not until all the possible risk and benefits of the procedures have been determined [23].

Having addressed the risk of LDRT for inflammatory/degenerative musculoskeletal disorders it should be noted that the other modalities of treatment are not without side effects or complications. The complications of surgery and anesthesia are known. Intrathecal steroid injection could result in infections, necrosis, tendon rupture and side effects due to the systemic effects of steroids [17,61]. One widely accepted modality for treating these conditions is stem cell transplantation. The side effects of this include graft versus host disease, susceptibility to infection and non-malignant organ or tissue dysfunction [62]. Extracorporeal shock wave therapy (ESWT) is associated with effects which are not limited to transitory reddening of the skin, pain, small hematomas, migraine and syncope [63]. Moreover, a randomized trial comparing ESWT to LDRT found both to be of equal efficacy [64,65].

Conclusion

Literature showed that many countries in Europe, especially Germany use radiation routinely for the treatment of many degenerative disorders including osteoarthritis with good results and few side effects. With LDRT for OA of the knee resulting in an effective dose equivalent to an abdominopelvic CT scan. Considering how recalcitrant to treatment degenerative skeletal conditions can be, LDRT is proven to be a reasonable and acceptable treatment option. A pilot study is therefore recommended with a view to establish the effectiveness or otherwise of this treatment method in regions of the world that have not adopted it.

Conflict of Interest

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

References


45. Mahmood S, Vu K, Tai P, et al. Radiation-induced second malign-
Radiotherapy for inflammatory disorders

Clinical management of uveal melanoma: a comprehensive review with a treatment algorithm

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Introduction

Melanoma is a malignancy that originates from the neoplastic proliferation of melanin-producing cells known as melanocytes, which can be primarily found in the skin, ocular region and mucous membranes. Uveal melanoma (UM) is the most frequently occurring non-cutaneous melanoma and is the most common primary intraocular malignancy in adults [1]. The uveal tract, a layer underlying the sclera of the eye, includes the iris, ciliary body and choroid. Around 95% of uveal melanomas arise from the choroidal melanocytes.

1. Epidemiology

The worldwide incidence of UM is estimated to be close to 4 to 5 cases per million per year and varies with gender, race and geographical location. Even though most studies reveal no apparent gender preponderance, some European studies have seen a slightly increased incidence in males [2]. Caucasians are most commonly affected ethnic group, accounting for 98% of UM cases. An increase in incidence of UM with latitude has also been observed with a decreasing gradient of cases from Northern to Southern Europe being reported. Furthermore, lower incidences of UM have also been noted in Asian and African nations [3].

2. Etiopathogenesis

As with many other types of malignancies, the precise causative elements for this rare cancer have yet to be clearly established. Both genetic and environmental risk factors have been implicated...
in the etiology of developing UM. Genetic factors previously associated include fair skin, inability to tan and light eye color [4]. A positive family history of UM, increased frequency of ocularmelanocytosis, BAP1 mutations and dysplastic nevi have also been linked to a higher incidence of UM [5]. Although sunlight exposure is an independent risk factor in the development of cutaneous melanoma, epidemiological attempts to analyze the association between exposure to ultraviolet (UV) light and UM have led to contradicting results. Some studies suggest that UV light exposure is a synergistic risk factor for developing UM in individuals with light iris color [6]. Mutation mechanisms with GNAQ and GNA11 signatures noted in illuminated areas of the uvea have also suggested that sunlight exposure may be an independent risk [7]. However, as previously stated, other attempts to associate intermittent and chronic UV light exposure with development of UM have led to inconsistent results [8]. The ability of the cornea and lens to filter a major portion of UV radiation in sunlight before it reaches the uveal tissue has been suggested as a possible explanation for this unclear association [9]. Finally, occupational hazards, such as welding, have also been associated as an etiologic source for developing UM as it usually involves additional chemical exposure along with both infrared and visible radiation.

3. Clinical features
Nearly half of the patients at the time of diagnosis are asymptomatic and UM is only identified after routine eye examination. Symptomatic patients present with ophthalmological features such as floaters, photopsia, visual field defects, metamorphopsia, visible tumor, and/or painful loss of vision [10]. Iris melanomas are diagnosed almost 15–20 years earlier than choroidal or ciliary body melanomas, primarily owing to early iris color changes and distortion of the pupil.

4. Diagnosis
There are significant differential diagnoses of UM that include choroidal nevus, retinal pigment epithelium hyperplasia and disciform degeneration, making it is integral to obtain an accurate diagnosis as soon as possible. A fundoscopy examination is the first step in obtaining this goal. Presence of orange pigment, subretinal fluid, and documentation of tumor growth aid in obtaining an appropriate diagnosis [11]. Further evaluation is needed for additional tumor characterization with procedures such as optical coherence tomography ultrasound and/or fluorescein angiography. Ultrasound features of UM include an intrinsic acoustic quiet zone and decreased internal reflectivity of the tumor. Usually, the tumor is often described as circumscribed mushroom or dome-shaped mass after rupture of the Bruch’s membrane of the retina [12]. Fluorescein angiography helps to evaluate the vascular supply of the tumor. A biopsy is not required for diagnosis, but is often performed for prognostic purposes. An understanding of the molecular structure of the tumor helps in risk stratification and determining initial treatment paradigms.

5. Prognosis
Despite advances in UM therapies, almost half of the patients are ultimately at risk for developing metastatic disease, primarily due to the inability to identify a unique feature of UM which is early micro-metastases [13]. Owing to this frequent subsequent presentation, patients diagnosed with UM require periodic surveillance with physical examination, blood tests and radiographic imaging such as CT, MRI, abdominal ultrasound or PET/CT. The most common initial distant metastatic sites include the liver followed by the lung, skin and bone. Ciliary body involvement, older age, epithelioid subtype and large tumor basal diameters are tumor features associated with poor prognosis [14]. Recent knowledge of detailed molecular mechanisms underlying UM has led to more accurate prognostic predictions. The 8q gain mutation has been associated with increased risk of metastasis while monosomy 3 has been associated with a decreased risk [15]. Additionally, gene expression profiling has proven to be a superior predictor of prognostic and metastatic potential in UM. Finally, detection of circulating tumor DNA is another important predictive factor for developing metastasis [16].

Given this constantly evolving treatment paradigm, herein, we evaluate the published data on local therapeutic options for non-metastatic UM and propose a functional treatment algorithm (Fig. 1).

Treatment Modalities
Most common treatment options for non-metastatic UM include surgery, plaque brachytherapy, and/or particle beam radiotherapy (RT). Surgical options include local resection, enucleation and orbital exenteration. Local resection can be achieved either by exoresection, which involves en bloc tumor removal via a scleral approach, or by enucleation, which is piecemeal removal via a vitreoretinal approach. These eye-conserving treatment approaches, in recent years, are now preferred over enucleation [17]. Enucleation is the surgical removal of the eye itself sparing the extraocular muscles and remaining orbital contents. Orbital exenteration involves the surgical removal of the entire orbital tissue including the eye, periorbita, appendages and eyelids. It is the preferred surgical approach for patients with large extraocular invasion or orbital extension. One added benefit of a surgical therapeutic ap-
approach is the ability to obtain adequate tissue samples for a detailed histopathologic and genetic analyses.

Plaque brachytherapy or plaque radiotherapy is the most widely used treatment modality in the management of UM and involves administration of a fixed dose of RT to the tumor. This is achieved by insertion of a radioactive implant into the episcleral tissue that delivers an apex RT dose of 80–100 Gy [18,19]. The most frequently employed radioisotope in the treatment of UM is Iodine-125 (\(^{125}\)I) owing to its favorable dosimetric profile, followed by Ruthenium-106 (\(^{106}\)Ru), and Palladium-103 (\(^{103}\)Pd) [20]. The most common complications of brachytherapy administration are retinopathy, cataract formations, macular edema, neovascular glaucoma, dry eye, keratitis, eye pain, and scleral necrosis. Finally, improved early outcomes have been noted in UM patients when brachytherapy administration has been aided with the use of additional techniques such as intraoperative ultrasound guidance and echographic confirmation of plaque placement [21].

Particle beam therapy (PBT) or charged-particle radiotherapy (CPRT) is the second most frequently used form of RT in the treatment of UM. Protons, helium ions and carbon ions are delivered as highly precise external RT beams with a pre-specified dose. When PBT is utilized, a RT dose of 50–70 cobalt gray equivalent (CGyE) is usually delivered in 4 to 5 fractions. When carbon ions are used, a dose of 60–85 CGyE is delivered in 4 to 5 fractions. Owing to their physical properties, charged particles provide increased targeting, especially at the end of the beam range [22]. Furthermore, the usage of tantalum chips and volumetric planning in three dimensions also lead to optimal dosage administration. However, in spite of a precise homogenous dose delivery to the tumor, CPRT can also cause damage to the surrounding normal ocular structures leading to toxicities such as maculopathy, retinal detachment, glaucoma, cataract, vitreous hemorrhage and papillopathy [23].

**Current Treatment Strategies based on Size of UM Tumor**

The overall tumor size for UM is assessed based on both the apical height as well as the largest basal diameter of the tumor and is classified based on guidelines from the Collaborative Ocular Melanoma Study (COMS) group [24].

1. **Small tumors**

   A landmark COMS study elucidated that tumors measuring <3 mm in apical height along with having a basal diameter measuring <5 mm should be primarily managed with observation [24]. There was no difference seen between patients enrolled in the study who received immediate therapeutic intervention versus those who pursued close observation and therefore the conclusion was to reserve treatment only at the time of tumor growth. Only 21% of patients on this trial demonstrated tumor growth in 2 years while 31% had tumor growth at 5 years post diagnosis.

2. **Medium tumors**

   Medium tumors are defined as an apical height of 3–8 mm and a basal diameter of <16 mm. Treatment options for these patients range from plaque brachytherapy to PBT to enucleation. Another landmark COMS study, conducted over a span of 10 years, evaluated the quality of life after \(^{125}\)I plaque brachytherapy (IBT) or enucleation in 209 patients with choroidal melanoma. They concluded that there was no significant difference in survival between the two groups, but revealed that there was better visual function, defined as peripheral vision, for up to 2 years after treatment in pa-
patients who underwent IBT when compared to enucleation [25].

Several other studies have been conducted with an aim to explore the use of different radioisotopes in plaque brachytherapy for UM [26–30] (Table 1). Verschueren et al. [30], analyzed the long-term outcomes of $^{106}$Ru brachytherapy in 425 patients with small or intermediate UM. They observed a 5-year local control (LC) and overall control of 96% and 79.6%, respectively and also revealed functional and cosmetic eye preservation rates at 5 years of 52% and 96%, respectively. Takiar et al. [28] also demonstrated excellent tumor control and acceptable toxicity levels after $^{106}$Ru brachytherapy in a cohort study of 40 patients with UM. Actuarial 5-year LC and overall survival were 97% and 92%, respectively. Enucleation was not required in any of the patients and there was no diagnosis of neovascular glaucoma at follow-up. Tarmann et al. [29] evaluated the medical records of 143 patients managed with $^{106}$Ru brachytherapy for UM and demonstrated excellent rates for tumor control with a 2- and 4-year recurrence rate of 8.4% and 14.7%, respectively. They also revealed promising eye-preservation results with the likelihood of keeping the eye in 94.7% of the patients at 24 months and 91.8% at 48 months post-brachytherapy. $^{103}$Pd plaque brachytherapy was evaluated by Finger et al. [26] in a retrospective case series of 400 patients with UM. They concluded that $^{103}$Pd provided a superior option compared to alternative forms of radiation and demonstrated a local control of 96.7%; only 14 patients in the study required enucleation at a later date. Larger trials are needed to ascertain the optimal dosage of IBT in the treatment of UM.

Finally, more recent data is emerging, looking at additional treatment options in conjunction with IBT. Use of intravitreal bevacizumab at the time of plaque removal and at 4-month intervals for a period of 2 years in 292 patients with UM showed significantly decreased macular edema and vision loss in these patients [31]. Additionally, a prospective non-comparative interventional case series by Shields et al. [27] in 270 patients with choroidal melanoma studied the effectiveness of IBT followed by transpupillary thermotherapy (TTT). TTT is a non-invasive treatment option where infrared lasers are delivered to the tumor and is mostly effective for smaller low-risk tumors [32]. Shields et al. [27] demonstrated that plaque brachytherapy followed by 3 sessions of TTT resulted in a tumor recurrence of only 2% at 2-year follow-up and 3% at 5-year follow-up.

Stereotactic photon beam radiosurgery (SRS) is another option that can be employed in the treatment of UM in the medium-sized tumor group. Gamma knife, CyberKnife or linear accelerator platforms are some of modalities utilized [33]. Sikuade et al. [34] conducted a review of 191 patients with UM who were managed with either SRS (n = 85) or PBT (n = 106). They concluded that both treatments had excellent LC rates and eye preservation rates (98% and 95% of SRS and PBT groups, respectively), but there was superior visual prognosis in the PBT group when compared to SRS (65% vs. 45%; p = 0.008).

### 3. Large tumors

Several studies have been performed to compare the effectiveness of surgical procedures to brachytherapy in the management of large UM, defined as an apical height > 8 mm or a basal diameter of > 16 mm [35–38] (Table 2). The most notable therapies utilized are CPRT and enucleation. That being said, IBT is also considered a potential option for large tumors. A large retrospective, comparative, non-randomized study of 237 patients with large UM (defined as thickness > 7.5 mm) by Bechrakis et al. [35], compared IBT to transscleral tumor resection (TSR) and demonstrated better visual acuity was retained in the TSR group (61.1% vs. 5.6%; p < 0.0009) as well as lower incidence of secondary glaucoma in TSR group when compared to IBT (5.6% vs. 33.3%; p = 0.03). There was no difference, however, in the mortality rates between the two groups. A matched case-control study by Kivela et al. [37], compared the complication rates, tumor control and visual acuity following IBT to TSR in 49 pairs of patients with large choroidal melanomas (thickness > 6 mm). The results of this study suggested that the risk of losing 20/200 vision was higher after IBT compared to TSR (hazard ratio [HR] = 2.38; 95% confidence interval [CI], 1.46–3.83; p < 0.001) but there was a lower risk of tumor recurrence after IBT compared to TSR (HR = 0.02; 95% CI, 0.01–0.11; p < 0.001). A

![Image](https://doi.org/10.3857/roj.2020.00318)

### Table 1: Studies of plaque brachytherapy in uveal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Radioisotope</th>
<th>n</th>
<th>Tumor thickness (mm)</th>
<th>Tumor diameter (mm)</th>
<th>Follow-up (yr)</th>
<th>Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shields et al. [27]</td>
<td>$^{125}$I (TTT)</td>
<td>272</td>
<td>4.0</td>
<td>11.0</td>
<td>5</td>
<td>97.0</td>
</tr>
<tr>
<td>Verschueren et al. [30]</td>
<td>$^{106}$Ru</td>
<td>425</td>
<td>4.2</td>
<td>10.9</td>
<td>5</td>
<td>96.0</td>
</tr>
<tr>
<td>Takiar et al. [28]</td>
<td>$^{106}$Ru</td>
<td>40</td>
<td>3.1</td>
<td>9.6</td>
<td>5</td>
<td>97.0</td>
</tr>
<tr>
<td>Tarmann et al. [29]</td>
<td>$^{106}$Ru</td>
<td>143</td>
<td>4.5</td>
<td>11.0</td>
<td>4</td>
<td>85.3</td>
</tr>
<tr>
<td>Finger et al. [26]</td>
<td>$^{103}$Pd</td>
<td>400</td>
<td>N/A</td>
<td>NA</td>
<td>4.2</td>
<td>96.7</td>
</tr>
</tbody>
</table>

I, iodine; Ru, ruthenium; Pd, palladium; TTT, transpupillary thermotherapy; NA, not available.

Table 2 shows additional comparisons of treatment options for large UM, including CPRT, enucleation, and SRS, among other options. The results highlight the importance of individual patient characteristics and tumor characteristics in determining the most appropriate treatment strategy. Further research is needed to refine the selection criteria for each treatment option and to identify optimal treatment strategies in the management of large UM.
A retrospective study by Puusaari et al. [38], in 87 patients with large UM compared TSR to IBT revealed promising results for improving visual acuity in the TSR group but also noted an increase in rates of local recurrence. They observed that the 2-year incidence of losing 20/400 vision was 60% (95% CI, 35–75) for TSR group and 75% (95% CI, 59–86) for IBT group but the risk of 5-year local recurrence in TSR group and IBT group was 41% (95% CI, 17–63) and 7% (95% CI, 2–17), respectively. The Zimmerman-McLean-Foster hypothesis suggests that rates of tumor recurrence is higher after surgical intervention of UM due to tumor manipulation during the procedures which may accelerate tumor cell dissemination [39,40]. Despite this hypothesis, given improved visual acuity and equivalent survivals, TSR has been advocated as an alternative to enucleation and RT in the treatment of large uveal melanomas [41,42].

Regarding CPRT, there are many studies detailing the use of PBT in comparison with other treatment modalities for UM [34,43-46] (Table 3). Abrams et al. [47] conducted a survival analysis of 1,004 cases of UM in which 380 cases were managed with external beam radiotherapy (EBRT) and 624 cases were managed with plaque brachytherapy. No difference in 5-year overall survival was seen between the two groups (83.3% EBRT vs. 82.5% BT; p = 0.69). Cajollé et al. [44] performed a retrospective study in 886 patients with UM who were managed with PBT. They observed LC rates of 93.9% and 92.1% at 5 and 10 years, respectively and also noted ocular conservation rates of 91.1% and 87.3% at 5 and 10 years, respectively. A prospective, interventional, noncomparative study performed in 2645 patients by Egger et al. [45], analyzed eye preservations rates in patients managed with PBT and found that overall eye retention rates were 88.9%, 86.2%, and 83.7% at 5, 10, and 15 years, respectively. They concluded that favorable results were noted even for larger tumors and tumors near the optic disc. A retrospective, consecutive cohort study in 492 patients with large UM by Bensoussan et al. [43], noted good LC with overall and specific survival rates at 5 years of 65% and 75%, respectively. They concluded that PBT can serve as an effective alternative to enucleation in patients with large tumors. The UCSF-LBNL randomized trial by Mishra et al. [46] conducted in 184 patients with UM, included 86 patients receiving Helium ion particle therapy and 98 patients receiving IBT. They noted significantly improved LC in particle arm compared to the IBT arm (100% vs. 84% at 5 years, 98% vs. 79% at 12 years; log-rank p = 0.0006). Significantly lower need for further enucleation was also demonstrated in particle arm (11% vs. 22% at 5 years, 17% vs. 37% at 12 years; log-rank p = 0.01). Given numerous prior studies revealed promising results, CPRT is now used as a definitive treatment option in large tumors. Furthermore, CPRT gains an obvious advantage when the UM is in a circumappapillary location surrounding the optic nerve, as it is not feasible to place a plaque completely around the tumor and hence CPRT is preferred. Additionally, in large tumors where IBT is not appropriate, CPRT is the preferred treatment modality over enucleation when eye preservation is desired [48].

Finally, Bechrakis and Foerster [49] developed a novel approach of combining neoadjuvant PBT and subsequent endoresection in 58 patients with large UM (thickness > 7 mm). They concluded that high-risk patients did not have increased morbidity and showed a lower rate of ocular side effects such as cataracts and retinal detachment in short-term follow-up compared to patients with UM.

### Table 2. Studies of TSR vs. IBT in uveal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Tumor height&lt;sup&gt;a&lt;/sup&gt; (mm)</th>
<th>Tumor diameter&lt;sup&gt;a&lt;/sup&gt; (mm)</th>
<th>VA in TSR and IBT</th>
<th>Risk of LR in TSR and IBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bechrakis et al. [35]</td>
<td>237</td>
<td>9.4</td>
<td>14.5</td>
<td>VA &gt; 2/200 in 61.1% TSR vs. 5.6% IBT (p &lt; 0.0009)</td>
<td>NA</td>
</tr>
<tr>
<td>Kivela et al. [37]</td>
<td>98</td>
<td>7.9</td>
<td>NA</td>
<td>VA &lt; 20/200 after IBT (HR = 2.38; 95% CI, 1.48–3.83; p &lt; 0.001)</td>
<td>LR in IBT vs. TSR (HR = 0.02; 95% CI, 0.01–0.11; p &lt; 0.001)</td>
</tr>
<tr>
<td>Caminal et al. [36]</td>
<td>72</td>
<td>10.0</td>
<td>15.0</td>
<td>VA &lt; 20/200 in 46.7% TSR vs. 68.8% IBT (p &lt; 0.121)</td>
<td>LR in TSR 10.5% vs. IBT 5.7% (p &lt; 0.602)</td>
</tr>
<tr>
<td>Puusaari et al. [38]</td>
<td>87</td>
<td>10.8</td>
<td>13.3</td>
<td>VA &lt; 2/400 in 60% TSR (95% CI, 35–75) vs. 75% IBT (95% CI, 59–86)</td>
<td>5-year LR 41% in TSR (95% CI, 17–63) vs. 7% in IBT (95% CI, 2–17)</td>
</tr>
</tbody>
</table>

TSR, transscleral resection; IBT, Iodine-125 brachytherapy; VA, visual acuity; LR, local recurrence; HR, hazard ratio; CI, confidence interval; NA, not available.

<sup>a</sup>Mean values.

### Table 3. Studies of external beam radiotherapy in uveal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Radiation</th>
<th>n</th>
<th>Mean follow-up (yr)</th>
<th>Local control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra et al. [46]</td>
<td>Helium ions</td>
<td>86</td>
<td>14.6</td>
<td>100 (5 yr)</td>
</tr>
<tr>
<td>Sikuade et al. [34]</td>
<td>I plaque</td>
<td>98</td>
<td>12.3</td>
<td>84 (5 yr)</td>
</tr>
<tr>
<td>SRS</td>
<td>106</td>
<td>2.8</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Caujolle et al. [44]</td>
<td>Protons</td>
<td>886</td>
<td>5.3</td>
<td>94 (5 yr)</td>
</tr>
<tr>
<td>Egger et al. [45]</td>
<td>Protons</td>
<td>2,645</td>
<td>3.6</td>
<td>99 (5 yr)</td>
</tr>
<tr>
<td>Bensoussan et al. [43]</td>
<td>Protons</td>
<td>492</td>
<td>5.1</td>
<td>94 (5 yr)</td>
</tr>
</tbody>
</table>

I, iodine; SRS, stereotactic radiosurgery.
of smaller size (thickness < 7 mm). A retrospective interventional case series by Willerding et al. [50], also studied the benefits of neoadjuvant PBT prior to TSR in 106 patients with UM. Local recurrence was noted in 5 patients while enucleation was required in 10 patients. The study concluded that there were no significant risk factors noted for local recurrence but also stated that additional vitreoretinal surgery was frequently needed (69.8%).

In summary, surgical intervention such as enucleation is the preferred approach in large tumors which cannot be effectively managed with RT, especially if they are well-circumscribed or juxtapapillary in location. The use of neoadjuvant RT prior to performing surgery has been shown to produce improved results and a decrease in the potential risk of tumor seeding. Further evaluation of this combined modality approach is required but may be appropriate patients presenting with neovascular glaucoma, tumor replacing more than half of the globe, orbital invasion or optic nerve involvement.

**Conclusion**

UM, the most common primary intraocular malignancy, continues to provide daunting challenges in its treatment management. With more than half the patients developing metastatic disease after initial non-metastatic presentation, prompt diagnosis and treatment play a crucial role in alleviating the morbidity and mortality of this disease. Currently, RT is the most common treatment approach in the management of UM, especially for small and intermediate-sized tumors. IBT is the most frequently employed type of RT, followed by CPRT. The most common surgical approaches remain enucleation and local resection. In recent years, enucleation is considered as an option only in patients with large tumors or in those with optic nerve involvement where RT does not result in a favorable outcome. The popularity of local resection has also diminished of late, as RT provides a superior alternative; however, when local resection is performed as a primary treatment modality, it is often coupled with neoadjuvant or adjuvant RT to further decrease chances of local recurrence. Additional clinical trials and targeted therapies aimed at the molecular pathogenesis of UM may offer novel avenues in managing this disease in the future.

**Conflict of Interest**

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

**References**

43. Bensoussan E, Thariat J, Maschi C, et al. Outcomes after proton...


Purpose: This study aimed to compare the current status of the national health insurance system (HIS) for advanced radiation technologies in Korea and Japan. Materials and methods: The data of the two nations were compared according to the 2019 guidelines on the application and methods of medical care benefit from the Ministry of Health and Welfare of Korea and the 2020 medical fee points list set by the Ministry of Health, Labor and Welfare of Japan. Results: Both countries have adopted the social insurance system and the general payment system which is fee-for-service for radiotherapy. However, for proton and carbon ion therapy, the Japanese system has adopted a bundled payment system. Copayment for radiotherapy is 5% in Korea and 30% (7–69 years old) in Japan, with a ceiling system. A noticeable difference is that additional charges for hypofractionation, tele-radiotherapy planning for an emergency, tumor motion-tracking, purchase price of an isotope, and image-guided radiotherapy are allowed for reimbursement in the Japanese system. There are some differences regarding the indication, qualification standards, and facility standards for intensity-modulated radiation therapy, stereotactic body radiation therapy, and proton therapy. Conclusion: Patterns of cancer incidence, use of radiotherapy and infrastructure, and national HIS are very similar between Korea and Japan. However, there are some differences in health insurance management systems for advanced radiation technologies. Keywords: National health insurance, Intensity-modulated radiation therapy, Stereotactic body radiation therapy, Proton therapy, Korea, Japan

Introduction

Patterns of cancer incidence and the role of radiotherapy in cancer treatment are very similar between Korea and Japan [1,2]. While 45% to 55% of patients with cancer have access to a well-developed radiotherapy infrastructure in the Western countries, in Korea and Japan, 25% to 30% of cancer patients are treated with radiotherapy [3-5]. However, there are some differences and similarities in radiotherapy infrastructure and organization patterns between Korea and Japan. Radiotherapy infrastructure showed fragmentation in both nations with a mixed pattern of capital centralization and fragmentation in non-capital areas in Korea, while in Japan, it showed uniform regional distribution [6-8]. Characteristics of both nations’ universal health insurance sys-
tem (HIS) are: (1) covering all citizens with social insurance, (2) easy access to medical institutions, and (3) high-quality medical services with low costs and have reached the world’s highest level of life expectancy and met the healthcare standards [9,10]. However, there are some differences regarding the indication, qualification standards, and facility standards for reimbursement for advanced radiation technologies [11–13].

This study aimed to compare the characteristics and patterns of the HIS for advanced radiation technologies between Korea and Japan by focusing on technologies such as intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and particle therapy.

Materials and Methods

We compared characteristics, patterns of the HIS, specific indications, and facility qualification for advanced radiation technologies between Korea and Japan, focusing on IMRT, SBRT, intracavitary radiotherapy (ICR), proton, and carbon ion therapy. Furthermore, we compared both nations’ data according to the 2019 guidelines on the application and methods of medical care benefit from the Ministry of Health and Welfare of Korea and the 2020 medical fee points list set by the Ministry of Health, Labor and Welfare of Japan [11–13]. As the cost of insurance treatment between the two countries varies greatly due to social and economic differences, simple comparison of treatment fee was excluded from this study.

Results

In Korea and Japan, healthcare service payment in radiotherapy is mainly based on a fee-for-service system. Both the Japanese health insurance system (JHIS) and the Korean health insurance system (KHIS) require the insured and dependents who receive healthcare services to pay copayment that is a part of total healthcare expenses. In KHIS, the copayment for cancer patients is 5% for all. Meanwhile, copayments in JHIS differ according to age and income status: 10% for 75 years or older (active income earner, 30%), 20% for 70 to 74 years (active income earner, 30%), 30% for 7 to 69 years, and 20% for 6 years or less, respectively. Patients (18 years or younger) with specific chronic pediatric diseases including cancer can be supported according to this income. For pediatric radiotherapy, additional treatment costs ranging from 20% to 80% are recognized depending on age in both systems (Table 1). Both have a copayment ceiling to adequately protect patients from catastrophic healthcare expenditures.

The maximum permissible radiotherapy sites and radiotherapy planning for reimbursement during a course of treatment are two in JHIS and three in KHIS, respectively. In JHIS, unlike in KHIS, additional charge for hypofractionation, tumor motion tracking, and IGRT are allowed. Recently, in JHIS, tele-radiotherapy planning for emergency treatment by other institutions has been allowed if there is a lack of suitable manpower (Table 2).

JHIS covers the cost of IMRT for only localized solid malignant tumors, while KHIS covers for metastatic lesions as well. In JHIS, the minimum conditions of IMRT using multi-leaf collimators are defined as follows: (1) more than three portals, (2) more than three intensity-modulated beams per portal, and (3) inverse planning. In JHIS, IMRT is reimbursed when the following personnel are present: (1) two full-time radiation oncologists and a radiotherapy technician, each with more than 5 years of radiotherapy experience and (2) an individual responsible solely for precision control of the radiotherapy devices, irradiation plan verification, and assistance with the irradiation plan (e.g., a radiotherapist or other technician). In KHIS, there are no specific qualifications and facility standards. In both systems, healthcare service payment in IMRT is mainly based on a fee-for-service system that consists of the cost of plan-

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Table 1. General comparison of national health insurance system in cancer patients between Japan and Korea

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>General payment system</td>
<td>Fee for service in general&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fee for service</td>
</tr>
<tr>
<td>Copayment</td>
<td>≥75 yr: 10% (active income earner: 30%)</td>
<td>5% of total treatment cost for registered cancer patients</td>
</tr>
<tr>
<td></td>
<td>70–74 yr: 20% (active income earner: 30%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7–69 yr: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≤6 yr: 20%</td>
<td></td>
</tr>
<tr>
<td>Copayment ceiling system</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Additional charge for pediatric radiotherapy</td>
<td>Neonate: 80%</td>
<td>≤1 yr: 50%</td>
</tr>
<tr>
<td></td>
<td>≤3 yr (excluding neonate): 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–5 yr: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–14 yr: 20%</td>
<td></td>
</tr>
</tbody>
</table>
|<sup>a</sup>Bundle payment for proton and carbon ion therapy.

https://doi.org/10.3857/roj.2020.00703
ning, treatment, and immobilization device. In JHIS, additional costs for hypofractionated IMRT (daily dose 250 cGy or more) for prostate cancer, and in IGRT costs for tumor tracking are allowed (Tables 3, 4).

ICR treatment costs consist of the cost of each part of JHIS, but in KHIS, the cost for the entire treatment is ceilinged. In Korea, the total cost for 5 or more fractionations of ICR is the same. However, in JHIS, unlike in KHIS, extra-charge for image-guided planning and the purchase price of the isotope have been added to the cost of the treatment as one-time for the entire course of the high dose rate ICR (Table 5). Specific indications for SBRT covered by both countries are relatively similar regarding the organs. Oligo-metastases for SBRT is defined by five sites or less in both systems. General indication for tumor size for SBRT is defined by 5 cm or less in JHIS. The details have been presented in Table 6.

JHIS for proton and carbon ion therapy has been adopted as a bundle or package price. Proton therapy for pediatric solid tumor is covered by the HIS in both countries. However, there are some differences in specific indications and facility qualifications for proton therapy in both countries. In JHIS, indication for proton and carbon ion therapy covered by health insurance are defined as follows: (1) pediatric solid tumor; (2) localized inoperable bone and soft tissue sarcoma; (3) head and neck cancers (except squamous cell cancer of oral cavity, larynx, and pharynx); and (4) prostate cancer. However, KHIS has adopted a wider range of indications (Table 7). If the treatment decision for proton or carbon ion therapy is made through a multidisciplinary tumor board, then the additional treatment fee is recognized in JHIS.

Table 2. General comparison of national health insurance system for RT in cancer patients between Japan and Korea

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily examination fee for outpatient RT</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Maximum allowable RT sites for reimbursement during a course of treatment</td>
<td>Two (50% price for 2nd site except IMRT, SBRT, and particle therapy)</td>
<td>Three (100% price for all site)</td>
</tr>
<tr>
<td>Maximum allowable RTP during a course of treatment</td>
<td>Twice (Same price except SBRT and particle therapy)</td>
<td>Three times (50% fee from 2nd plan)</td>
</tr>
<tr>
<td>Additional charge for hypo fractionation</td>
<td>Yes for prostate and breast cancer RT</td>
<td>No</td>
</tr>
<tr>
<td>Remote RTP for emergency</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Extra charge for tumor motion tracking</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Extra charge for IGRT</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

RT, radiotherapy; RTP, radiotherapy planning; IGRT, image-guided radiation therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Table 3. Comparison of national health insurance system for IMRT utilization, and facility qualification between Japan and Korea

<table>
<thead>
<tr>
<th></th>
<th>Japan</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Limited solid malignant tumor$^a$</td>
<td>Solid tumor (primary, metastatic cancer, and CNS benign tumors)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Re-RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Boost therapy</td>
</tr>
<tr>
<td>Three most common cancers using IMRT and utilization</td>
<td>In 2014–2018 survey, (1) prostate cancer, (2) head and neck cancer, (3) CNS tumor</td>
<td>In 2018 survey, (1) breast cancer, (2) lung cancer, (3) prostate cancer</td>
</tr>
<tr>
<td></td>
<td>15% in 2017 survey</td>
<td>23% in 2016 survey</td>
</tr>
<tr>
<td>Qualification standards</td>
<td>Two or more full-time radiation oncologists, at least one of them with RT experience for 5 years or more</td>
<td>Not specified</td>
</tr>
<tr>
<td>Facility standards</td>
<td>Linear accelerator</td>
<td>Not specified</td>
</tr>
<tr>
<td></td>
<td>Planning CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inverse RT planning system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Equipment restricting patient movement and of organs within the body</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Micro-ionization chamber or semiconductor dosimeter (including diamond dosimeter) and water phantom or equivalent solid phantom</td>
<td></td>
</tr>
</tbody>
</table>

IMRT, intensity-modulated radiation therapy; CNS, central nervous system; RT, radiotherapy; CT, computed tomography.

$^a$Metastatic lesion is not permitted.
Discussion and Conclusion

Both Japan and Korea have adopted the social insurance system which enables rapid and easy access to medical care with low cost for all citizens and meets the world's highest level of life expectancy and healthcare standards. In countries adopting a tax-financed system, it is pointed out that citizens cannot choose a medical institution and waiting time to access medical care is generally long. For example, in the UK, general physicians (registered family physicians) are in charge of primary medical care. However, it is a problem as the waiting time is too long [9,10]. Fee-for-service payments are calculated by multiplying the price per score and resource-based relative value scores (RBRVS) based on the amount of work and resources such as manpower, facilities, equipment, and risks of medical treatments and the fee charged for each activity. The Ministry of Health and Welfare of Korea determines RBRVS. In Japan, the medical service fees grading table is used to evaluate costs by grading individual technologies and services, determined...
by the Ministry of Health, Labor, and Welfare [11,12].

For the hypofractionated three-dimensional whole breast radiation (daily 2.5 Gy or more) instead of a conventional dose (46 to 50 Gy in 23 to 25 fractions), additional treatment cost is permitted in JHIS based on the randomized clinical results, which can reduce the number of hospital visits and the load on radiotherapy institutes [14]. In JHIS, tele-radiotherapy planning for emergency treatment is allowed if there is a lack of suitable manpower. This tele-radiotherapy planning for an emergency by another institution can be used to help with emergency treatment at poorly staffed treatment facilities.

The utilization rate of IMRT is steadily increasing. In Japan, it was 15% in 2017, while in Korea it was 23% in 2016 [15,16] (Table 3). There are some differences regarding the indication, qualifications, and facility standards for IMRT between two countries. JHIS covers the cost of IMRT for only localized solid malignant tumors, while KHIS covers for metastatic lesions as well. Oligo-metastasis may be considered as an indication for IMRT in KHIS. According to the Japanese Society for Radiation Oncology database report of 2018, IMRT was mostly used to treat prostate, head and neck, and central nervous system tumors in Japan [17]. However, in Korea, IMRT was most commonly used to treat breast, lung, and prostate cancers in 2018 [13].

JHIS adopted stricter indications for proton and carbon ion therapy (Table 7). Although the American Society for Radiation Oncology did not recommend proton therapy for prostate cancer outside of a prospective clinical trial, it is covered by JHIS [18]. However, in JHIS, the cost of proton therapy for prostate cancer is cheaper than other treatments and is set to be similar to the total cost of IMRT. If the treatment decision for proton or carbon ion therapy is made through a multi-disciplinary tumor board the additional treatment fee is recognized in Japan.

In conclusion, patterns of cancer incidence, infrastructure, and HIS are very similar between Korea and Japan. However, there is a considerable difference regarding the additional charges for hypofractionation, tumor motion tracking, and purchase price of an isotope among others. Furthermore, there are some differences regarding the indication, qualification standards, and facility standards for IMRT, SBRT, and proton therapy.

Conflict of Interest

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

References


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Management of symptomatic radiation necrosis after stereotactic radiosurgery and clinical factors for treatment response

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Purpose: Approximately 10% of patients who received brain stereotactic radiosurgery (SRS) develop symptomatic radiation necrosis (RN). We sought to determine the effectiveness of treatment options for symptomatic RN, based on patient-reported outcomes.

Materials and Methods: We conducted a retrospective review of 217 patients with 414 brain metastases treated with SRS from 2009 to 2018 at our institution. Symptomatic RN was determined by appearance on serial magnetic resonance images (MRIs), MR spectroscopy, requirement of therapy, and development of new neurological complaints without evidence of disease progression. Therapeutic interventions for symptomatic RN included corticosteroids, bevacizumab and/or surgical resection. Patient-reported therapeutic outcomes were graded as complete response (CR), partial response (PR), and no response.

Results: Twenty-six patients experienced symptomatic RN after treatment of 50 separate lesions. The mean prescription dose was 22 Gy (range, 15 to 30 Gy) in 1 to 5 fractions (median, 1 fraction). Of the 12 patients managed with corticosteroids, 6 patients (50%) reported CR and 4 patients (33%) PR. Of the 6 patients managed with bevacizumab, 3 patients (50%) reported CR and 1 patient (18%) PR. Of the 8 patients treated with surgical resection, all reported CR (100%). Other than surgical resection, age ≥54 years (median, 54 years; range, 35 to 81 years) was associated with CR (odds ratio = 8.40; 95% confidence interval, 1.27–15.39; p = 0.027).

Conclusion: Corticosteroids and bevacizumab are commonly utilized treatment modalities with excellent response rate. Our results suggest that patient’s age is associated with response rate and could help guide treatment decisions for unresectable symptomatic RN.

Keywords: Brain, Radiosurgery, Necrosis
Introduction

There has been an increase in the incidence of brain metastases over the years with an estimated 100,000 to 240,000 people diagnosed each year in the United States, almost 10 times greater than the incidence of primary brain tumors [1]. Increased incidence of brain metastases is believed to be secondary to an earlier detection through improved diagnostic techniques in addition to newer systemic therapies which allow patients to live longer with metastatic disease [2]. Despite these newer therapies/detection modalities, once the primary neoplasm has metastasized to the brain, despite multimodal treatment, the outcomes are usually poor [3].

The approach to management in these cases varies depending on multiple factors such as the site, type and staging of the primary tumor, the size and number of metastases along with the age and performance status of the individual. The main therapeutic options for brain metastases include surgical resection, whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and/or systemic therapy such as immunotherapy. SRS is slowly emerging as a popular therapeutic option due to its short and convenient treatment course, high rates of local controls, and its relative mitigation of neurocognitive deficits when compared to WBRT [4]. Despite the many benefits seen with SRS, it is not without adverse effects, including radiation necrosis (RN) a late toxicity usually observed months to years postsRS [5].

RN is an inflammatory reaction leading to irreversible necrotic degeneration of the brain tissue at the site of previous cerebral irradiation [6]. The management of RN depends on the symptomatic presentation which can vary from mild symptoms such as nausea or headaches to more severe symptoms such as cognitive or neurological deficits and seizures. While smaller, asymptomatic RN can be managed with observation and careful monitoring, larger more symptomatic RN must be treated definitively with various therapeutic options such as corticosteroids, bevacizumab, surgical resection, or some combination of above.

Corticosteroids act by modulating inflammatory changes and edema, often leading to rapid symptomatic improvement after initiation [7]. However, steroid toxicity and withdrawal pose dosing-related challenges and complications. Bevacizumab, a monoclonal antibody which inhibits vascular endothelial growth factor A (VEGF-A), hinders angiogenesis and has shown benefit in symptomatic RN cases [8]. Surgical resection of the necrosed tissue also effectively manages RN but also has its disadvantages as it is an invasive procedure [9]. Each of therapeutic modality has its own relative benefits and drawbacks. In this study, we have aimed to evaluate the effectiveness of these three therapeutic options in the management of symptomatic RN, utilizing patient-reported outcomes.

Materials and Methods

We conducted an IRB-approved retrospective review of patients with brain metastases who were treated with SRS at Acibadem Maslak Hospital between 2009 to 2018 (No. 20191116). The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients were treated with robotic linear accelerator (CyberKnife, Sunnyvale, CA, USA)-based SRS. Demographic, clinical, and brain lesion information was collected, including age, gender, location of brain metastases, number of brain metastases, tumor size, tumor volume, addition of WBRT, and prescription dose.

A post-SRS brain magnetic resonance imaging (MRI) was obtained 4 to 6 weeks after treatment followed by serial MRIs every 3 months thereafter. At each follow-up visit, RN was rated according to the Radiation Therapy Oncology Group (RTOG) CNS toxicity criteria with diagnosis being determined on serial MRIs, MR spectroscopy, and development of new CNS/neurologic complaints without evidence of disease progression [10].

The management of RN depends on the symptomatic presentation which can vary from mild symptoms such as headaches to more severe symptoms such as cognitive or neurological deficits and seizures. In this study, symptomatic RN was managed with corticosteroids alone, bevacizumab and/or surgical resection at the discretion of the treating physician. Patients who received bevacizumab and those who underwent surgical resection received a trial of corticosteroids first. Once diagnosed, patients were seen 2–4 weeks after treatment of symptomatic RN and then subsequently followed with appropriate diagnostic imaging and clinical follow-up every 3 months. At last follow-up visit, patients graded the RN treatment outcomes as complete response (CR), partial response (PR), and no response (NR). The primary endpoint was to determine the patient-reported response rate with treatment of symptomatic RN. Statistical analyses were performed using SPSS statistical software version 25 (IBM Corp., Armonk, NY, USA).

Results

We identified 414 brain metastases treated with SRS in 217 patients at our institution from 2009 to 2018. Twenty-six patients experienced symptomatic RN after treatment of 50 lesions (Table 1). Median follow-up was 10.1 months (range, 6.2 to 100.0 months) since SRS. Median number of RN per patient was 1 (range, 1 to 4). Median patient age was 54 years (range, 35 to 81 years). Most common histologies were primary non-small cell lung cancer (69%) and breast cancer (23%). Median tumor size was 0.77 cm (range, 0.01 to 1.96 cm). The most common metastases location was parietal lobe (40%), occipital lobe (30%), and temporal lobes (18%).
mean prescription dose was 22 Gy (range, 15 to 30 Gy) in 1 to 5 fractions (median, 1 fraction). WBRT was received by 66% of the patients either before or after SRS. Among the patients with symptomatic RN, RTOG CNS grade 2 toxicity was observed in 19 patients (73%) and grade 3 in 7 patients (27%) (Table 2). The main symptoms were headache in 20 patients (77%), muscle weakness in 3 patients (11%), seizures in 2 patients (8%), and cognitive impairment in 1 patient (4%).

Patients with symptomatic RN lesions were managed by one of three treatment modalities namely oral corticosteroids (n = 12), bevacizumab (n = 6) or surgical resection (n = 8). Median follow-up was 8.5 months (range, 3.2 to 96.0 months) since treatment of symptomatic RN. A total of 17 patients (66%) reported CR, 5 patients (19%) reported PR, and 4 patients (15%) reported NR. Among the 12 patients managed with corticosteroids, 6 patients (50%) reported CR, 4 patients (33%) PR, and 2 patients (17%) reported NR. Among the 6 patients managed with bevacizumab, 3 patients (50%) reported CR, 1 patient (18%) reported PR, and 2 patients (33%) reported NR. Among the 8 patients treated with surgical resection, all reported CR (100%). Other than surgery, factor associated with CR on univariate logistic regression was age ≥54 years (median, 54 years; range, 35 to 81 years; odds ratio = 8.40; 95% confidence interval, 1.27–15.39; p = 0.027) (Table 3).

Discussion and Conclusion

SRS has emerged as an important therapy in the management of brain metastases and over the years has evolved into its own therapeutic option as opposed to adjunctive treatment after WBRT [11–13]. The goal of SRS is to achieve a more effective therapeutic response by administering a higher dose of radiation per fraction while reducing the integral dose to normal brain parenchyma. The utilization of SRS is dictated by the clinical scenario in question and it can be employed in a variety of forms such as a planned boost post-WBRT, a conformally administered adjuvant treatment after surgical resection, and/or as single-modality treatment as well [14].

Though SRS is considered an effective treatment option for limited brain metastases with decreased neurocognitive deficits compared to WBRT, it is not without its own toxicities. RN is one such
Management of symptomatic radiation necrosis

rare but serious long-term effect of SRS, occurring in around 5%-25% of patients who have been treated with SRS [15]. It usually presents as a late complication 6 to 18 months after SRS and can manifest in a variety of presentations including incidental detection on routine imaging to seizures, headaches, and/or with focal neurologic deficits. History of prior radiation exposure, dose of radiation administered, volume of brain parenchyma irradiated, concurrent systemic therapy and intrinsic radio-sensitivity of the primary histology are all risk factors in the development of RN [16]. The primary underlying pathophysiological mechanism for the development of necrosis is believed to be due to radiation-induced injury of the cerebral blood vessels which leads to secondary brain parenchymal damage. Another theory suggests direct radiation-induced damage to glial cells resulting in white matter demyelination and necrosis [17].

The treatment options for RN are often determined based on its clinical presentation of symptoms. Asymptomatic RN is typically managed with observation with close clinical and radiological monitoring, whereas symptomatic RN often necessitates active treatment [18,19]. Corticosteroids, humanized monoclonal antibodies against VEGF, anticoagulants, hyperbaric oxygen therapy, and surgical resection are some of the available treatment options for the management of RN.

Corticosteroids have long been considered the first line treatment option for symptomatic RN, with several trials demonstrating their benefit. They provide benefit in patients with RN by reducing inflammatory changes and decreasing the permeability of the blood-brain barrier [7]. The adverse effects associated with long-term steroid use such as gastric ulceration, steroid-induced myopathy, iatrogenic Cushing syndrome, and steroid toxicity are major drawbacks associated with this treatment [20]. Another option which has generated significant interest in the management of RN is bevacizumab, which is a monoclonal antibody against VEGF. The upregulation of vascular inflammatory changes, which plays a crucial role in the pathophysiology of RN, can be modulated by administration of this drug [8,21]. A randomized placebo-controlled double-blind trial conducted by Levin et al. [22] presented Class I evidence for bevacizumab as a treatment option for RN. The administration of bevacizumab has been tempered due to some of the adverse effects of this drug, such as thrombosis, hemorrhage, and impaired wound healing.

In patients who are refractory to treatment with corticosteroids or bevacizumab, surgical resection can be considered as a treatment option. Surgical resection provides the benefit of prompt symptomatic relief by decreasing mass effect and relieving intracranial pressure, in addition to providing confirmation of diagnosis via histopathological evaluation. A retrospective study conducted by Telera et al. [23] concluded that surgical resection in a group of 15 patients with symptomatic RN provided symptomatic relief in 14 patients. The high risk of morbidity associated with surgical resection of the lesion, however, is often a deterrent in choosing this option. This potential risk of morbidity has been highlighted in a study conducted by McPherson et al. [9] which emphasized that surgical intervention should be reserved as an option only in treatment-refractory RN.

Limitations of our study include its small sample size, retrospective design, and inherent confounding factors that cannot be completely accounted for in a non-randomized study. In addition, patient-reported therapeutic outcomes were graded using a non-validated questionnaire which may be influenced by patient’s background and desirability of answer.

Studies comparing three modalities of treatment of RN, such as corticosteroids, bevacizumab and surgical resection are relatively rare. In our study, we have aimed to further shed light on this aspect and have concluded that corticosteroids and bevacizumab are commonly utilized treatment modalities in our institution with a 50% CR rate. Our results also indicate that the patient’s age is associated with response rate and could help guide treatment decisions for unresectable symptomatic RN.

Conflict of Interest

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

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The effect of deep inspiration breath–hold technique on left anterior descending coronary artery and heart dose in left breast irradiation

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Purpose: To determine the effect of the deep inspiration breath–hold (DIBH) technique on left anterior descending coronary artery (LAD) region and heart dose in left breast cancer irradiation.

Materials and Methods: Twenty-five left breast cancer patients who previously received breast-conserving surgery underwent computed tomography (CT) simulation with both free-breathing (FB) and DIBH techniques and four radiation treatment plans. The plan comprised the following with both the FB and DIBH techniques: whole breast (WB), and WB with internal mammary lymph nodes (WB+IMNs). The prescription dose was 50 Gy in 25 fractions. The doses to the LAD region, heart and lungs were compared. Moreover, in-field maximum heart distance (maxHD) and breast volume were analyzed for correlations with the mean heart dose (MHD).

Results: In the WB plan with DIBH vs. FB techniques, the mean radiation doses to the LAD region, MHD, and the left lung V_20 were 11.48 Gy vs. 19.84 Gy (p < 0.0001), 2.95 Gy vs. 5.38 Gy (p < 0.0001), and 19.72% vs. 22.73% (p = 0.0045), respectively. In the WB+IMNs plan, the corresponding values were 23.88 Gy vs. 31.98 Gy (p < 0.0001), 6.43 Gy vs. 10.24 Gy (p < 0.0001), and 29.31% vs. 32.1% (p = 0.0009), respectively. MHD correlated with maxHD (r = 0.925) and breast volume (r = 0.6).

Conclusion: The use of the DIBH technique in left breast cancer irradiation effectively reduces the radiation doses to the LAD region, heart and lungs. MHD is associated with maxHD and breast size.

Keywords: Breast cancer, Radiation, Coronary vessels, Heart dose, Deep inspiration breath–hold

Introduction

Breast cancer is the most common female cancer among women in Thailand and worldwide [1,2]. With technical advancements, the treatment outcome, quality of life and survival of breast cancer patients have been much improved. Currently, radiotherapy remains an important modality in breast cancer treatment. Radiation therapy either after breast-conserving surgery or postmastectomy significantly reduces recurrence risk and mortality [3,4]. Recently, internal mammary node (IMN) irradiation has been increasingly used after its overall survival benefit was shown [5,6].

Although breast irradiation improves survival in breast cancer patients, cardiac complications are of concern especially in left breast irradiation. Adding IMN irradiation with a wide tangential field could increase the radiation exposure to the heart. Darby et al. [7] reported that the rate of major coronary events increased by 7.4% per Gray (Gy) of the mean radiation dose to the heart (mean heart dose [MHD]) without a minimum dose threshold. MHD has been commonly used when evaluating the effect of radiation on the heart. Recently, the radiation dose to left anterior descending coronary artery...
(LAD) and other substructures has also been studied [8].

Aiming to minimize radiation doses to normal tissues in breast cancer patients, the deep inspiration breath-hold (DIBH) technique has been extensively studied [9]. The DIBH technique expands the lungs and moves diaphragm downward, which in turn moves the heart posteriorly and inferiorly. This maximizes the distance between the chest wall and the heart during or close to deep inspiration; consequently, reduces radiation exposure to the heart.

Effects of the DIBH technique in reducing the radiation dose to the LAD have recently been reported [10-13]; however, delineation of the LAD requires an injection of a contrast agent, which is not usually performed in our clinical practice. We contoured the anterior interventricular groove from its origin down to the apex of the heart as the LAD region. This study intended to study the effect of the DIBH technique on reducing the radiation dose to the LAD region and heart in left breast cancer patients.

Materials and Methods

1. Patient selection and simulation
After obtaining approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (No. 409/60), we prospectively enrolled patients with left sided breast cancer who underwent breast-conserving surgery, had a good performance status (Eastern Cooperative Oncology Group [ECOG] 0–1), and could perform breath holding. Either Philips Brilliance Big Bore or Siemens SOMATOM Definition CT (computed tomography) was used for simulation in our division. In the CT simulation, a breast board was used to immobilize the patients while both arms were up. The patients underwent two series of CT simulation scans; free-breathing (FB) and DIBH without an intravenous contrast injection (Fig. 1A, 1B). Radiopaque markers were placed on the patient’s chest to indicate the field borders. The medial and lateral borders were at the midline and mid-axillary line, respectively. The upper border was the lower border of the clavicular head, and the lower border was approximately 1–2 cm below the inframammary fold. A CT scan during FB was performed first, followed by a DIBH scan. For the DIBH scan, the patients were trained to perform a deep inspiration and then hold their breath for approximately 20 seconds. We provided a teaching video clip to the patients so that they could study the concept of the DIBH and practice how to hold their breath during CT scans and treatments [14]. The stability of patient’s breath holding status was monitored by the Varian Real-time Position Management (RPM) respiratory gating system during the CT simulation and by the AlignRT (VisionRT, London, UK) during daily treatments. The CT slice thickness was 3 mm, and the

![Fig. 1](https://doi.org/10.3857/roj.2020.00094)
axial images were constructed with 3-mm spacing.

2. Treatment planning

Each patient underwent four treatment plans, covering the whole breast (WB) and WB plus IMNs of the first to third intercostal spaces (WB+IMNs) with both FB and DIBH techniques. To make the target volume coverages comparable, tangential whole breast radiotherapy (WBRT) fields with both breathing techniques utilized the same surface markers that defined the medial, lateral, superior and inferior borders (Fig. 1C, 1D). In WB+IMNs plans, clinical target volume (CTV) was delineated according to the Radiation Therapy Oncology Group (RTOG) breast contouring guidelines [15]. The planning target volume (PTV), 5-mm expansion from the CTV, was used to define the treatment field (Fig. 2). The WB+IMNs plans were normalized until 95% of PTV receiving at least 45 Gy. Additionally, 95% of the target volume dose had to be no more than 1 Gy different between the FB and DIBH plans, as shown in dose volume histogram in Fig. 3. Forward intensity-modulated radiotherapy (IMRT) using an electronic compensator was applied in all plans. The prescription dose was 50 Gy in 25 fractions. The final dose distribution was calculated using Eclipse treatment planning system with inhomogeneity correction (Eclipse version 11.0.31). Normal structures including the heart, lungs and the LAD region were also contoured in both FB and DIBH images. The LAD region was contoured according to RADCOM atlas [16] (Fig. 4).

The cardiac parameters were mean LAD region dose, MHD, heart V25 and heart V40. The lung parameters included left lung V20 and mean bilateral lungs. In-field maximum heart distance (maxHD), which was measured in centimeters on digitally reconstructed radiograph from CT images, was recorded and analyzed to determine whether this parameter correlated with MHD. The In-field maxHD values from all four plans, WB plans and WB+IMNs plans with both FB and DIBH techniques were used to study their correlations with the MHD. Breast volume (measured in cm³) from FB images of WB and WB+IMNs plan were used to study the correlation with the MHD.

Dosimetric parameters of the mean LAD region and heart and lung doses were compared using a two-tailed paired t-test. MaxHD and breast size were evaluated and analyzed using Spearman rank test to determine correlations with MHD.

Results

From March 2017 to November 2018, 25 left breast cancer patients who met the inclusion criteria were recruited. For both the WB and the WB+IMNs irradiation groups, compared with the FB
Fig. 3. Dose volume histogram of the planning target volume (PTV) of the WB+IMNs plan with the FB technique (A) and the DIBH technique (B). The WB+IMNs plans were normalized until 95% of PTV received at least 45 Gy. To be comparable, 95% of the target volume dose was no more than 1 Gy different between the FB and DIBH plans; this patient received 45.37 Gy and 45.96 Gy with the FB and DIBH plans, respectively.

WB, whole breast; IMN, internal mammary node; FB, free-breathing; DIBH, deep inspiration breath-hold.

Fig. 4. The contouring method of the left anterior descending coronary artery (LAD) region. The anterior interventricular groove was contoured from the origin of the LAD (A) down to mid heart (B) and continuing to the apex of the heart.

Table 1. Radiation doses to the normal tissues of the WB plans with the FB and DIBH techniques

<table>
<thead>
<tr>
<th>Respiratory management</th>
<th>DIBH</th>
<th>FB</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LAD region (Gy)</td>
<td>11.48 ± 8.1 (2.6–29.0)</td>
<td>19.84 ± 10.2 (4.0–45.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean heart (Gy)</td>
<td>2.95 ± 2.3 (1.1–7.2)</td>
<td>5.38 ± 3.5 (2.0–14.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart V25 (%)</td>
<td>3.48 ± 4.4 (0.0–14.7)</td>
<td>8.20 ± 7.1 (1.4–25.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart V40 (%)</td>
<td>2.48 ± 3.7 (0.0–9.3)</td>
<td>6.22 ± 5.9 (0.0–21.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lung parameter</td>
<td></td>
<td></td>
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<tr>
<td>Mean bilateral lungs (Gy)</td>
<td>5.02 ± 1.0 (3.6–7.0)</td>
<td>5.45 ± 1.4 (4.0–9.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Left lung V20 (%)</td>
<td>19.72 ± 4.3 (13.5–28.0)</td>
<td>22.73 ± 6.1 (14.5–39.0)</td>
<td>0.0045</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range).

WB, whole breast; FB, free-breathing; DIBH, deep inspiration breath-hold; LAD, left anterior descending coronary artery.
Discussion and Conclusion

Advanced radiation technologies have contributed to the better treatment outcomes and longer survival of breast cancer patients. However, radiotherapy also has late treatment side effects, especially on the heart and coronary arteries in left-sided breast cancer patients. Therefore, recent studies have focused on techniques, especially the DIBH technique, that can reduce radiation doses to the heart and LAD.

In this study, we used an electronic compensator technique for the adjuvant radiation of breast cancer since this technique could achieve better homogeneity index as well as lower dose to the organs at risk [17]. Although the multileaf collimator could reduce cardiac dose, this study did not use it in order to assess the actual benefits of the DIBH technique over the FB technique. We found that the radiation doses to cardiac parameters were significantly reduced with the DIBH technique, similar to the results of previous studies [9-11,18-21]. In the WB plans, the MHD was reduced from 5.38 Gy in FB to 2.95 Gy in DIBH (45.2% reduction) (Table 1). Similarly, in the WB+IMNs plans, the MHD was also significantly reduced from 10.24 Gy with the FB technique to 6.43 Gy with the DIBH technique (37.2% reduction) (Table 2).

In addition to MHD, volumes of the heart receiving high doses, heart V25 and heart V40, have been used to determine the radiation dose. In the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) study, a heart V25 of < 10% led to a less than 1% long-term cardiac mortality rate [22]. In our study, the heart V25 was less than 10% with both the FB and the DIBH techniques for the WB plans. In the WB+IMNs plans, although the heart V25 with both the FB and DIBH techniques were more than 10%, the value was reduced from 16.9% with the FB technique to 10.3% with the DIBH technique.

Table 2. Radiation doses to the normal tissues of the WB + IMNs plans with the FB and DIBH techniques

<table>
<thead>
<tr>
<th>Respiratory management</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>DIBH</td>
</tr>
<tr>
<td>Mean LAD region (Gy)</td>
<td>23.88 ± 10.6 (4.2–45)</td>
</tr>
<tr>
<td>Heart parameter</td>
<td></td>
</tr>
<tr>
<td>Mean heart (Gy)</td>
<td>6.43 ± 3.8 (1.7–12.7)</td>
</tr>
<tr>
<td>Heart V25 (%)</td>
<td>10.37 ± 8.0 (0.3–29.0)</td>
</tr>
<tr>
<td>Heart V40 (%)</td>
<td>7.50 ± 6.0 (0.0–18.0)</td>
</tr>
<tr>
<td>Lung parameter</td>
<td></td>
</tr>
<tr>
<td>Mean bilateral lungs (Gy)</td>
<td>7.16 ± 1.5 (4.3–10.1)</td>
</tr>
<tr>
<td>Left lung V25 (%)</td>
<td>29.31 ± 6.0 (20.0–42.0)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range).

WB, whole breast; IMN, internal mammary node; FB, free-breathing; DIBH, deep inspiration breath-hold; LAD, left anterior descending coronary artery.

Fig. 5. (A) Correlation between in-field maximum heart distance and MHD in both the WB and WB+IMNs plans. (B) The differences of MHD between the FB and DIBH techniques (MHD of the FB – MHD of the DIBH) in both the WB and WB+IMNs plans. The horizontal lines above the boxes are the 75th percentile + 1.5xIQR. The upper border, the line inside, and the lower border of the box represent the 75th, 50th, and 25th percentiles, respectively. The horizontal lines below the boxes are the 25th percentile – 1.5xIQR. The three dots represent outliers (>75 percentile + 1.5xIQR). MHD, mean heart dose; WB, whole breast; IMN, internal mammary node; FB, free-breathing; DIBH, deep inspiration breath-hold; IQR, interquartile range.
Although the parameters of the radiation dose to the whole heart, including MHD, heart \( V_{25} \) and heart \( V_{40} \), have been widely used, radiation doses to other sub-structures of the heart, such as the LAD, have been proposed to be a potentially better parameter of coronary events. The BACCARAT study reported that the left ventricle and LAD were the most radiation-exposed structures during left breast irradiation \([8]\). Therefore, the LAD dose may correlate with ischemic heart disease.

Previous studies found that the DIBH technique could reduce the radiation dose to the LAD \([9,11,20]\). Contouring of the structures significantly affects the calculated radiation doses. Duane et al. \([23]\) developed a cardiac contouring atlas for 15 cardiac segments, including 10 coronary arterial segments. However, the atlas needs contrast-enhanced images. After the contouring is standardized, the dose constraint to each structure can be developed. In our practice, we do not use radiation contrast; therefore, the LAD cannot be precisely determined. Instead we delineated the anterior interventricular groove from its origin down to the apex of the heart as the LAD region, according to the RADCOM study \([16]\). We found that in the WB plan, the radiation doses to the LAD region decreased from 19.84 Gy with the FB technique to 11.48 Gy with the DIBH technique (42.1% reduction) (Table 1). Similarly, in the WB+IMNs plans, the radiation doses also significantly reduced from 31.98 Gy with the FB technique to 23.88 Gy with the DIBH technique (25.3%) (Table 2). Currently, the dose constraint to the LAD region has not been determined. Some of our patients received mean LAD doses as high as 50 Gy (Table 2). Beaton et al. \([24]\) reported that a maximum LAD dose of less than 45.4 Gy correlated with lower cardiac mortality. Since our study is a dosimetric study, a long-term follow-up study is needed to determine the clinical impact of the cardiac and LAD dose reductions.

Regarding lung doses, we found that all lung parameters were lower in the DIBH plans than in the FB plans (Tables 1, 2), similar to previous studies \([10,11,20]\). We did not include supraclavicular (SPC) field in the WB+IMNs plan in this study since the lung dose from SPC field would not have large differences between the FB and DIBH plans. The typical beam direction for the SPC field is anteroposterior, and the DIBH technique cannot reduce the irradiated lung volume. In addition, the volume and motion of the upper lobe are less affected by breathing than those of other lobes. However, in our clinical practice, we routinely irradiate the SPC field in all patients who receive radiation to IMNs.

In addition, we found that the maxHD correlated with MHD (Fig. 5A), similar to a previous study \([25]\). Notably, to the best of our knowledge, our study is the first to show that breast size significantly correlated with MHD. Cardiac radiation exposure increased with larger breast sizes (Fig. 6). This is probably because large pendulous breasts would fall down posteriorly, forcing the posterior border of the tangential field to be wider.

In conclusion, the use of the DIBH technique in left breast cancer irradiation effectively reduces radiation exposure to the heart and LAD region in both the WB and WB+IMNs plans. MHD correlates with the maximum heart distance and breast size.

**Conflict of Interest**

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

**References**


Patterns of failure and clinical outcomes of post-operative buccal mucosa cancers treated with adjuvant ipsilateral radiotherapy

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Purpose: Adjuvant radiotherapy (RT) in buccal mucosa cancers is guided by histopathological factors. The decision to treat ipsilateral or bilateral draining lymph node is on physician discretion and guidelines do not have a defined indication regarding this. We aimed to analyze the failure patterns and survival in buccal mucosa cancers treated with adjuvant ipsilateral RT.

Materials and Methods: One hundred sixteen cases of post-operative buccal mucosa cancers—pT3 or more, node positive, close margins (1–5 mm), lymphovascular invasion positive, perineural invasion positive, depth of invasion >4 mm—treated with RT to primary and ipsilateral nodes from May 2013 to May 2019 were retrospectively analyzed. Patients were treated to a dose of 60–66 Gy (44 Gy in the first phase and a coned down boost of 16–22 Gy in the second phase) with three-dimensional conformal radiotherapy on a linear accelerator. Primary end point was to assess control rates and secondary end point was to evaluate the overall survival (OS) and disease-free survival (DFS) outcomes.

Results: Median age was 46 years with male; female ratio of 110:6. The edition of the American Joint Committee on Cancer stage distributions were I (3.4%), II (34.4%), III (24.1%), and IV (37.9%). At a median follow-up of 22 months, crude rates of local failure, regional failure, and contralateral neck failure were 9.4%, 10.3%, and 3.4%, respectively. The 2-year contralateral neck control rate was 94.9%. Pathological positive node portended poorer OS (86.6% vs. 68.6%; p = 0.015) and DFS (86.5% vs. 74.9%; p = 0.01).

Conclusion: Incidence of contralateral recurrence with ipsilateral irradiation in buccal mucosa cancers is low with descent survival outcomes, particularly in node negative cases.

Keywords: Adjuvant radiotherapy, Carcinoma, Mouth mucosa

Introduction

Oral cavity cancers account for approximately 0.35 million new cases and 0.18 million deaths annually, worldwide [1]. India accounts for roughly one-third of the new cases and around half the number of deaths [1]. Buccal mucosa cancers accounts for around half of these cancers [2,3]. Standard therapy for buccal mucosa cancers is optimal surgical resection followed by adjuvant treatment [4]. Adjuvant radiotherapy after surgery is indicated in cases with pathological tumor size of pT3 or more, pathological node
positivity, close margins, lymphovascular invasion (LVI) positive, perineural invasion (PNI) positive, depth of invasion (DOI) > 6 mm [5]. Around 60% cases of buccal cancers present with advanced stage and patients tend to have multiple risk factors [6,7]. Post-operative radiotherapy with or without chemotherapy is the standard of care after resection of locally advanced carcinomas, as these patients are higher risk for locoregional relapse [8]. The volumes for adjuvant radiotherapy generally include the primary tumor bed, ipsilateral and or contralateral nodal volumes. Standard guidelines regarding the inclusion or exclusion of contralateral draining lymph nodes as elective volume in adjuvant radiotherapy does not exist and are mostly guided by clinician discretion. For patients with clear margins and no extracapsular extension, elective contralateral neck radiation is suggested for cases with high risk like advanced disease approaching midline and multiple positive nodes in the ipsilateral neck which increase the risk of nodal recurrence in the contralateral neck [9]. However, contralateral neck irradiation is not routinely performed [9-11]. Various clinical studies opine that ipsilateral neck dissection results in good outcomes with very limited contralateral neck failure in buccal mucosa cancers [12,13] setting the pretext for ipsilateral adjuvant radiotherapy in selected subset of buccal mucosa cancers.

There are no detailed guidelines regarding the management of buccal cancers in terms of ipsilateral or bilateral neck irradiation. However, selected subset of buccal mucosa cancers presenting with limited number of risk factors and favourable prognosis can be treated with ipsilateral radiotherapy to neck nodes and tumor bed, thereby limiting toxicity but without impairing outcomes. Literature on patterns of failure in these group of patients is sparse. The general practice followed at our institute is to irradiate the ipsilateral face and neck in patients intermediate risk disease [14]. We therefore conducted a retrospective analysis of prognostic factors, failure patterns and survival outcomes in these cohort of buccal cancers treated with ipsilateral irradiation at our institute and tried to identify subgroup(s) with poor prognosis suitable for more aggressive therapeutic approach.

**Methods and Materials**

1. **Patients**
   It was a retrospective analysis of buccal mucosa squamous cell carcinoma patients, treated with surgery and radiotherapy to primary and ipsilateral nodes from May 2013 to May 2019. The data of 1,400 patients of head and neck cancer treated with radiotherapy was retrieved from the departmental archives of radiation oncology department. From this data, 116 cases of buccal mucosa cancers who underwent curative resection and received irradiation to primary tumor and ipsilateral neck were identified. The consort diagram representing the actual number of patient data retrieved has been mentioned in Fig. 1. All the records were reviewed for each patient: age, gender, site of primary tumor, stage as per the 7th edition of the American Joint Committee on Cancer [15], histological findings after surgery, local and regional recurrence in ipsilateral and contralateral neck, disease-free survival (DFS) and overall survival (OS). The patients receiving neoadjuvant chemotherapy were excluded. The patients having tumor in any site other than buccal mucosa and multiple oral cavity and/or head and neck cancers or previously treated oral cancers were also excluded from the study.

2. **Treatment**
   All patients underwent adequate resection of the primary tumor and neck nodes. Surgery of the primary tumor consisted of wide local excision or composite resection with/without marginal or segmental mandibulectomy depending upon the extent of the disease. Neck dissection included either supra-omohyoid or modified radical neck dissection. Patients with any or more of the following risk factors were included in the study: pathological tumor size of pT3 or more, pathological node positivity, close margins, LVI positive, PNI positive, DOI > 6 mm. While evaluating various outcomes in terms of DOI, < 12 mm and > 12 mm were use as parameters [13]. All patients had lateralized primary tumors with adequate surgical resection.

   Clinical target volumes (CTV) consisted of the post-operative tumor bed with a margin of 1 cm and the ipsilateral nodal volumes. The levels of the nodal volumes were decided as per the risk factors present in the post-operative histopathological factors and the possible sites of clinical and nodal spread. The planning target volumes for primary tumor and ipsilateral neck nodes were identified. The planning target vol-

![Fig. 1. Consort diagram depicting the selection of patients for the present analysis.](https://doi.org/10.3857/roj.2020.00458)
ume (PTV) included CTV with a 0.5-cm uniform margin to account for set up and motion errors. Radiotherapy was delivered using 6-MV photons to a dose of 60–66 Gy, using a 2-Gy dose fractionation, one fraction per day, 5 days per week by using linear accelerator (Infinity and Synergy; Elekta, Crawley, UK) with a collimator leaf width of 1 cm at the isocentre. Patients were treated with three-dimensional conformal radiotherapy using either parallel opposed anterior-posterior oblique fields in a single phase to a dose of 60–66 Gy respecting the spinal cord tolerance or using anterior and lateral field in two phases, in which 44 Gy was delivered in the first phase and a coned down boost of 16–22 Gy was delivered in the second phase. The median dose of radiotherapy was 60 Gy (range, 58 to 66 Gy). All patients were followed up on a regular basis: monthly once for first 6 months, every 2 months for the next year, every 3 months for the third and fourth years, and then 6 months to annually, thereafter.

3. Statistics
Primary end point was to assess local and regional control rates and secondary end point was to evaluate the survival outcomes: OS, DFS, and distant metastasis-free survival (DMFS). Locoregional failure was defined as the appearance of tumor in the post-operative bed or cervical node metastasis or both. All time intervals were calculated from the date of registration in the radiation oncology or surgical oncology department (whichever was earlier) to the date of event of interest. OS was measured from the date of registration to the date of death from any cause. DFS was defined as the time from the day of registration to date of failure (either locoregional or distant or both) or death. DMFS was defined as the time interval until the development of distant metastasis. Statistical analysis was performed with SPSS statistical software package for Mac (version 23.0; IBM, Armonk, NY, USA). All survival analyses were performed using Kaplan–Meier method. Log-rank test was used to test the statistical significance of differences in the survival and control rates. p < 0.05 was considered statistically significant. All potential prognostic factors were analyzed. Cox regression analysis was used to perform multivariate analysis on factors found significantly associated with outcomes in univariate analysis.

Results

1. Clinicopathological factors
Median age was 46 years (range, 28 to 80 years) with male; female ratio of 110:6. All patients underwent ipsilateral neck dissection, except three patients who underwent bilateral neck dissection. Stage of the patients in terms of pathological tumor size, pathological nodal size and overall pathological staging have been mentioned in Table 1. Four patients of stage I (pT1N0) were taken up for adjuvant radiotherapy as they had one or more high-risk factors for recurrence (two of them had PNI, one had lymphovascular space invasion and three patients had DOI more than 10 mm). Fifty-six patients (48.27%) had clinically positive nodes, but 48/116

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>64 (55)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>52 (45)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110 (95)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Tobacco addiction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>102 (87.9)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>69 (59.4)</td>
</tr>
<tr>
<td>pT stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>2</td>
<td>63 (54.3)</td>
</tr>
<tr>
<td>3</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>4</td>
<td>22 (19.0)</td>
</tr>
<tr>
<td>pN stage</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>68 (58.6)</td>
</tr>
<tr>
<td>1</td>
<td>37 (31.9)</td>
</tr>
<tr>
<td>2</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>Overall TNM stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>II</td>
<td>40 (34.4)</td>
</tr>
<tr>
<td>III</td>
<td>28 (24.1)</td>
</tr>
<tr>
<td>IV</td>
<td>44 (37.9)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>WD</td>
<td>59 (50.9)</td>
</tr>
<tr>
<td>MD</td>
<td>51 (43.9)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>DOI (mm)</td>
<td></td>
</tr>
<tr>
<td>&lt; 12</td>
<td>63 (54.3)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td>Risk factors for PORT*</td>
<td></td>
</tr>
<tr>
<td>pT3 or more</td>
<td>42 (36.2)</td>
</tr>
<tr>
<td>pN+</td>
<td>48 (41.4)</td>
</tr>
<tr>
<td>PNI</td>
<td>31 (26.7)</td>
</tr>
<tr>
<td>LVI</td>
<td>34 (29.3)</td>
</tr>
<tr>
<td>DOI</td>
<td>46 (39.7)</td>
</tr>
</tbody>
</table>

*p, pathological tumor stage, pN, pathological nodal stage; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; PNI, perineural invasion; LVI, lymphovascular invasion; DOI, depth of invasion; PORT, post-operative radiotherapy.

*aThe total may not add up to 100% due to multiple factors present in each patient.
(41.3%) were pathologically positive. The ipsilateral neck was irradiated in 113 cases (97.4%), whereas 3 cases received radiotherapy only to the primary tumor bed.

2. Locoregional control, local control, and regional control
Median follow-up was 22 months (range, 6 to 163 months). The 2-year locoregional control (LRC), local control (LC), and regional control (RC) rates were 80.9%, 88.4%, and 89.5%, respectively. There were 23 locoregional failures. The crude LC and RC rate were 90.5% and 89.7%, respectively. There was no significant difference in LRC, LC, and RC with clinicopathologic factors like age, sex, pT stage, overall tumor stage, LVI, PNI, DOI or grade (Table 2). There was statistically significant difference in 2-year LRC rates for different nodal stages (pN0 vs. pN1 vs. pN2: 86.1% vs. 71.5% vs. 77.9%; p = 0.036) (Fig. 2). The factor significantly influencing LRC rate (pN0 vs. pN1+2: 86.1% vs. 72.9%; p = 0.016) and RC rate (pN0 vs. pN1+2: 100% vs. 81.8%; p = 0.037) was pathological nodal staging, although it did not influence the LC rates.

3. Overall survival
The 2-year OS for the entire cohort was 79.5%. The number of

Table 2. Variation of outcomes with prognostic factors in univariate analysis

<table>
<thead>
<tr>
<th>Prognostic factor analyzed</th>
<th>OS</th>
<th>DFS</th>
<th>LRC</th>
<th>LC</th>
<th>RC</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT (1 vs. 2 vs. 3 vs. 4)</td>
<td>0.500</td>
<td>0.635</td>
<td>0.796</td>
<td>0.176</td>
<td>0.642</td>
</tr>
<tr>
<td>pN (0 vs. 1 vs. 2)</td>
<td>0.045*</td>
<td>0.032*</td>
<td>0.036*</td>
<td>0.185</td>
<td>0.031*</td>
</tr>
<tr>
<td>pN (0 vs. 1/2)</td>
<td>0.015*</td>
<td>0.010*</td>
<td>0.016*</td>
<td>0.136</td>
<td>0.037*</td>
</tr>
<tr>
<td>pTNM (1 vs. 2 vs. 3 vs. 4)</td>
<td>0.914</td>
<td>0.897</td>
<td>0.897</td>
<td>0.314</td>
<td>0.659</td>
</tr>
<tr>
<td>pTNM (1/2 vs. 3/4)</td>
<td>0.554</td>
<td>0.653</td>
<td>0.563</td>
<td>0.987</td>
<td>0.470</td>
</tr>
<tr>
<td>LVI (negative vs. positive)</td>
<td>0.064</td>
<td>0.159</td>
<td>0.268</td>
<td>0.062</td>
<td>0.911</td>
</tr>
<tr>
<td>PNI (negative vs. positive)</td>
<td>0.479</td>
<td>0.593</td>
<td>0.356</td>
<td>0.948</td>
<td>0.321</td>
</tr>
<tr>
<td>Grade (1 vs. 2 vs. 3)</td>
<td>0.804</td>
<td>0.808</td>
<td>0.683</td>
<td>0.132</td>
<td>0.927</td>
</tr>
<tr>
<td>Grade (1+2 vs. 3)</td>
<td>0.653</td>
<td>0.712</td>
<td>0.627</td>
<td>0.203</td>
<td>0.553</td>
</tr>
<tr>
<td>DOI ( &lt; 12 vs. ≥ 12 mm)</td>
<td>0.869</td>
<td>0.925</td>
<td>0.944</td>
<td>0.156</td>
<td>0.348</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.846</td>
<td>0.766</td>
<td>0.173</td>
<td>0.415</td>
<td>0.319</td>
</tr>
<tr>
<td>Age ( &lt; 50 vs. ≥ 50 yr)</td>
<td>0.453</td>
<td>0.371</td>
<td>0.582</td>
<td>0.162</td>
<td>0.542</td>
</tr>
</tbody>
</table>

OS, overall survival; DFS, disease-free survival; LRC, locoregional control; LC, local control; RC, regional control; pT, pathological tumor stage, pN, pathological nodal stage; LVI, lymphovascular invasion; PNI, perineural invasion; DOI, depth of invasion.
* p < 0.05.

Fig. 2. Kaplan-Meier curves depicting the variation of locoregional control with (A) pN (0 vs. 1 vs. 2) and (B) pN (0 vs. 1/2).
events in T1, T2, T3, and T4 were 4/11, 14/63, 3/20, and 4/22, respectively, for calculation of OS. On performing an univariate analysis, tumor stage, pathological tumor size, LVI, PNI and DOI didn’t impact the OS (Table 2). However, statistically significant results were noticed with pathological nodal staging. There was statistically significant improved outcomes with pathological node negativity. Presence of pathologically positive nodes was significantly inversely correlated with OS; (pN0 vs. pN1+2: 86.6% vs. 68.6%; p = 0.015; Fig. 3A) and (pN0 vs. pN1 vs. pN2: 86.6% vs. 71.7% vs. 64.9%; p = 0.045), respectively.

4. Disease-free survival
The 2-year DFS rate was 77.4%. The percentage of events in pN0, pN1, and pN2 cases for calculation of DFS were 11/68 (16%), 11/37 (30%), and 4/11 (36%), respectively. Among the prognostic factors, only pathological N staging was associated statistically significant decrease in 2-year DFS rates with nodal positivity; (pN0 vs. pN+: 86.5% vs. 74.9%; p = 0.010; Fig. 3B) and (pN0 vs. pN1 vs. pN2: 84.3% vs. 69.6% vs. 64.9%; p = 0.032), respectively.

5. Failure patterns
Twenty-three patients had locoregional failures. Of these 30.4% (7/23) cases failed within 12 months, while 60.8% (14/23) patients failed within 2 years. Eleven cases had isolated local failure without regional failure, while 12 had isolated local failure. Four patients had contralateral neck failures. Five patients had isolated distant failures. The crude contralateral lymph node failure (CLNF) rate and 2-year contralateral neck recurrence control rate were 3.4% (4/116) and 94.9%, respectively. The most significant factor affecting CLNF was nodal status. Statistically significant difference in CLNF rates were found with higher nodal burden (pN0 vs. pN1 vs. pN2: 100% vs. 97.1% vs. 71.4%; p = 0.001) and positive nodal status (pN0 vs. pN1+2: 100% vs. 86.3%; p = 0.009). On further analysis, it was found that 3 of 4 patients having contralateral neck failures had N2b disease. One patient with contralateral neck failure had N1 disease leading to a crude failure rate of 2.7% (1/37 patients). The histopathological feature of patients with contralateral neck failure were as follows: patient #1 (pT2N2b, PNI+, LVI+, moderately differentiated, clear margins, DOI 10 mm), patient #2 (pT4N1, PNI+, moderately differentiated, clear margins, DOI 6 mm), patient #3 (pT2N2b, moderately differentiated, clear margins, DOI 12 mm), and patient #4 (pT1N2b, well differentiated, clear margins, DOI 10 mm). All 4 patients had undergone a modified neck dissection. Statistically significant difference in ipsilateral nodal failure rates were found with higher nodal burden (pN0 vs. pN1 vs. pN2: 94.8% vs. 80.1%; p = 0.033) and positive nodal status (pN0 vs. pN1+2: 94.8% vs. 78.8%; p = 0.038). The crude distant failure rate was 4.3% (5/116). The 2-year DMFS was 95.4%.

6. Multivariate analysis
The prognostic factor significantly associated with poorer control rates, that is pN stage was further evaluated by Cox regression multivariate analysis. In the analysis of pN0 vs. pN+, p-value was found significant for OS (hazard ratio [HR] = 0.372; 95% confidence interval [CI], 0.16–0.85; p = 0.02) and DFS (HR = 0.356; 95% CI, 0.15–0.81; p = 0.04). Nodal stage N2 was associated with worst outcomes for OS, DFS, and LRC.
Discussion and Conclusion

This retrospective review aims to analyse prognostic factors and outcomes associated with the treatment of buccal mucosa cancers receiving ipsilateral radiotherapy in a tertiary cancer centre. Ghosal et al. [16] reported 80% oral cancers presenting with stage III and IV. Our cohort had similar findings at 67% advanced cancers at presentation. The decision of need for ipsilateral or bilateral neck radiotherapy is generally arrived upon after assessing the clinicopathological features in the post-operative histopathology and the risk of nodal drainage to ipsilateral and contralateral lymph nodes [8]. The risk of nodal metastasis leading to neck failure varies among different sites of oral cavity in the range of 30%–40% [17]. For buccal mucosa, the risk ranges from 10% to 30% [18-20], while for other sites like tongue it is generally mentioned in the range of 15%–75% [21-24]. Buccal cancers have higher neck control rates as compared to sites like tongue, as reported by Liao et al. [24], 5-year neck control rate of 93% versus 86% (p = 0.0115) in a retrospective comparison of buccal and tongue cancers.

Several authors have previously reported on unilateral radiation therapy in well-lateralized oral cavity and oropharyngeal cancers [10,13,18,25] with excellent outcomes in terms of survival and contralateral neck control, but limited reports have been published addressing outcomes in cases of buccal cancers treated with unilateral irradiation. Publications by Vergeer et al. [13] and Cerezo et al. 118] have reported 5-year OS rates of 61% and 82.5%, respectively, in a combined cohort of oral cavity and oropharyngeal malignancies. Both these studies included a mixed bag of patients, and hence the outcomes cannot be directly applied to a site like buccal mucosa, which is generally well lateralized. One of the larger studies focusing on outcomes of combined modality treatment in buccal mucosa cancers was reported by Lin et al. [8], who reported outcomes of 145 cases, of which 125 were treated with ipsilateral irradiation. The 5-year OS was 55%. However, it included all types of buccal mucosa cancers, including those with extracapsular extension which accounted for 31.7% patients warranting concurrent chemoradiotherapy. So, the inclusion of high risk patients may have resulted in inferior outcomes compared to the cohort of patients in the previously mentioned studies. Another report by Habib et al. [26] addresses the results of unilateral face and neck treatment in 481 oral cavity cancers, but only 165 cases received combined modality treatment. The current report is one of the first study addressing the outcomes of unilateral irradiation in buccal mucosa cancers.

The incidence of various prognostic factors was comparable to that of other studies, PNI was present in 26.7% [27], while moderately differentiated tumors were around 48%. DeConde et al. [27] have reported 29% incidence of PNI and moderately differentiated tumors were 48%. Diaz et al. [22] and Pop et al. [28] have reported the timing of locoregional failure to be 12 months or before 24 months. While most of the recurrences tend to happen within the first 2 years [16], the incidence of recurrence in neck varies from 5%–10% for early cancers [13] to 25%–30% in advanced cases [22]. Our outcomes also corroborate with the literature with most failures (63.6%) happening within 24 months. The current study failed to show a predictive relationship between pT stage and overall TNM stage. This could be attributed possibly to the fact that, the patients with early stage tumors, i.e., pT1/2 tumors were associated with more number of other poor prognostic factors and also that is the reason they received radiotherapy. Nodal staging was associated with significantly poor outcomes in terms of OS, DFS, and LRC. Pathological node positive (pN+) disease status was associated with statistically significant differences in OS, DFS, LRC, and RC, although pN+ status didn’t influence LC in our study. No significant differences were found in OS with LVI, PNI or grade, although there was a trend towards significant decrement in OS with LVI+ disease and grade.

There is paucity of literature addressing CLNF following unilateral neck surgery and irradiation in buccal cancers. The incidence of CLNF varies according to the site of primary tumor. For oral cavity cancers, it is reported to be 0.9%–36% [29-32]. However, for anatomical site like buccal mucosa which has drainage largely to ipsilateral lymph nodal regions, have negligible rates of contralateral lymph node recurrence ranging from 0%–5.7% (Table 3). The chances of CLNF increase with T stage [29-31]. However, some other studies suggest no variation in CLNF with T stage [13,32]. Several other studies mention variation with grade of the tumor [26,31,33,34] while one study by Kowalski et al. [28] suggests no association of CLNF with differentiation status. Presence of nodes draining ipsilaterally entail a poor prognosis and increase the risk of CLNF [13,26,32-36]. Twenty-seven percent (13/48) cases with pN+ disease had locoregional failures in our study. Four out of 48 pN+ cases (8.3%) had CLNF in our cohort. Capote-Moreno et al. [33] have reported similar outcomes with 21.6% patients showing contralateral neck failures in patients presenting with pN+ disease and 6.4% contralateral neck failure rates in ipsilateral nodal disease. Table 3 shows studies assessing various prognostic factors which affect the rate of involvement of contralateral lymph node in buccal mucosa cancers.

Ipsilateral radiotherapy decreases doses to contralateral salivary gland, thereby decreasing incidence of xerostomia [35]. The ipsilateral fields also cause decrease rates of mucositis as lower volumes of oral mucosa is irradiated [36]. There is growing evidence in the
Table 3. Studies depicting CLNF in buccal mucosa cancers and factors affecting it

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>OC cases</th>
<th>BM</th>
<th>Cohort</th>
<th>Incidence of CLNF</th>
<th>Factors increasing incidence of CLNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al. [8]</td>
<td>2008</td>
<td>142</td>
<td>All</td>
<td>BM only</td>
<td>3/142 (2.1)</td>
<td>Time to diagnosis (p = 0.03), clinical TNM staging, ipsilateral clinical N status (p = 0.04), grade (p = 0.04), margins (p = 0.007), type of neck dissection (p = 0.04), PNI (p = 0.0002)</td>
</tr>
<tr>
<td>Gonzalez-Garcia et al. [34]</td>
<td>2008</td>
<td>315</td>
<td>All</td>
<td>BM only</td>
<td>18/315 (5.7)</td>
<td>Gender, tumor location, homolateral positive nodes, tumor extension across the midline, histologic grade, margin status, pattern of growth, and perineural spread</td>
</tr>
<tr>
<td>Capote-Moreno et al. [33]</td>
<td>2010</td>
<td>OC + OPX 402</td>
<td>31</td>
<td>OC + OPX</td>
<td>23/296 (7.7) for OC, 1/31 (3.2) for BM</td>
<td>Poor differentiation, regional lymph node metastasis, ipsilateral nodal metastasis (p = 0.006)</td>
</tr>
<tr>
<td>Fang et al. [23]</td>
<td>2013</td>
<td>67</td>
<td>All</td>
<td>BM only</td>
<td>0/67 (0.0)</td>
<td>Poor differentiation, regional lymph node metastasis, ipsilateral nodal metastasis (p = 0.006)</td>
</tr>
<tr>
<td>Habib et al. [26]</td>
<td>2015</td>
<td>481</td>
<td>46</td>
<td>OC</td>
<td>14/481 (2.9), 2/46 (4.34) for BM</td>
<td>Multiple ipsilateral lymph node metastasis (N2b)</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td>116</td>
<td>All</td>
<td>BM only</td>
<td>4/116 (3.4)</td>
<td>Multiple ipsilateral lymph node metastasis (N2b)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
OC, oral cavity; BM, buccal mucosa; CLNF, contralateral lymph node failure; OPX, oropharynx; LVI, lymphovascular invasion; PNI, perineural invasion.

The literature that ipsilateral radiotherapy in oral cavity cancers is as good as bilateral radiotherapy, with better side effect profile [37]. The effectiveness of ipsilateral radiotherapy in a particular group of patients is because of low incidence of contralateral nodal involvement. In the previously published series by Lin et al. [8] which evaluated treatment outcomes in buccal mucosa cancers, it was opined by the authors that bilateral irradiation was given more to patients with N2 disease, but it conferred no significant benefit (p = 0.95) over unilateral radiotherapy in terms of LRC. Based on these facts, they recommend unilateral radiotherapy in cases with multiple lymph nodes.

Based on our results, we recommend that contralateral neck irradiation may be avoided safely in intermediate risk group of patients as per inclusion criteria of our study. We also recommend individualizing the balance between the risk of contralateral nodal failure and expected toxicity of bilateral irradiation while considering ipsilateral or bilateral irradiation in buccal mucosa cancers particularly in patients with multiple number or level of ipsilateral nodal involvement.

Certain limitations associated with this analysis have been enumerated. Firstly, the report is retrospective in nature. Secondly, we have reported the study with a median follow-up of 2 years, although it is worth considering that most of the failures happen within the first 2 years [16]. The above-mentioned limitations, however, highlight the importance of publishing single institutional data, which are eventually consolidated through meta-analysis. Moreover, this type of data is likely to come from retrospective studies only, thereby further highlighting the need to address this issue, so that we can exclude that cohort of patients from ipsilateral radiation which have high likelihood of failure, either locally or regionally, including ipsilateral and contralateral failures. Strength of the study includes a pure patient sample with homogenous uniform treatment, and to the best of our knowledge and as per the literature review the first such study addressing a ipsilateral radiotherapy in buccal mucosa cancers. This study will further add to the understanding of the pattern of failures and addresses the cohort of patients which might benefit the most by irradiation of the bilateral rather ipsilateral neck.

In conclusion, the incidence of contralateral recurrence in buccal mucosa cancer patients treated with primary surgery and adjuvant ipsilateral irradiation is low. It points to the fact that buccal mucosa carcinoma patients with intermediate risk factors can be spared of bilateral irradiation, without significantly affecting the OS and LRC rates. Patients with multiple pathologically involved nodes are at higher risk for developing contralateral regional recurrence as compared to node-negative disease.

Conflict of Interest

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

References


Introduction
Pediatric Hodgkin lymphoma (pHL) is a rare disease in Korea with a crude incidence of 1.3 per million among ages 0 to 14 years [1]. In the United States, pHL accounts for nearly 5%-10% of pediatric malignancies, with approximately 1,700 newly diagnosed cases among children under 20 years old [2]. Studies conducted in western countries report that pHL is a highly curable disease with 5-year event-free survival (EFS) and overall survival (OS) exceeding 90% [3]. However, the epidemiology and clinicopathologic features of Hodgkin lymphoma in Korea show discrepancies with the features of western countries [4].

Purpose: To analyze the clinical outcomes and long-term toxicity of pediatric patients with Hodgkin lymphoma after combined-modality treatment (CMT) with involved-field or involved-nodal radiotherapy (RT).

Materials and Methods: We retrospectively reviewed the records of 27 pediatric Hodgkin lymphoma patients who received CMT at a single institution between January 1990 and July 2017. Patients with stage I–III received a heterogeneous chemotherapy regimen depending on their risk group followed by 19.8–36 Gy RT, with the dose based on their response to the chemotherapy before RT. An optional 9–20 Gy boost was delivered to residual sites. The risk group was determined based on the initial stage, the presence of bulky disease, and any B symptoms. We evaluated overall survival, event-free survival, and long-term toxicities.

Results: A total of 27 patients completed the CMT. At a median follow-up of 125 months (range, 9 to 337 months), the estimated 5-year event-free survival and overall survival were 88.9% and 96.3%, respectively. Late symptomatic cardiopulmonary toxicity was not observed, and only one patient was positive on a subclinical obstructive pulmonary function test. The incidence of hypothyroidism was 58.3% among 12 patients with an available thyroid function test. There was one papillary thyroid cancer diagnosed 7.2 years after treatment.

Conclusion: CMT for pediatric Hodgkin lymphoma with involved-field and involved-nodal RT achieved an excellent survival with only modest long-term toxicity. Smaller-field RT seemed to decrease long-term toxicities and had good local control.

Keywords: Pediatrics, Hodgkin disease, Radiotherapy, Survival, Long-term adverse effects
over 90% [6-10]. Contemporary radiation techniques with involved-field radiotherapy (IFRT) or involved-nodal radiotherapy (INRT) have lower risks of long-term toxicities.

There are only a few studies that have reported on Hodgkin lymphoma, but most of them have included the entire age group due to the extremely low incidence of pHL in Korea. Only one study specifically reported the clinical features and survival of pediatric malignant lymphoma cases, including 18 patients with pHL, but no clinical data about the treatment modality or RT techniques were described [11]. Moreover, there is no report on the survival or treatment-related toxicities of pHL among pediatric and adolescent cases in Korea that received contemporary combined-modality treatment (CMT). Therefore, we observed the clinical outcomes and long-term toxicity of pediatric patients with Hodgkin lymphoma after CMT with IFRT or INRT in a single institute.

Materials and Methods

We reviewed the medical records of pediatric patients under 19 years old with Hodgkin lymphoma between January 1990 and July 2017. All patients were pathologically diagnosed with pHL by surgical biopsy or percutaneous lymph node biopsy. We excluded patients with (1) only a short-term follow-up period, or (2) mantle-field RT. Patients were included if they received CMT with chemotherapy followed by RT with IFRT or INRT. Approval by the Institutional Review Board of Asan Medical Center was obtained for this study (IRB No. 2018-0774).

Patients were physically examined and underwent chest X-ray and computed tomography (CT) of the neck, chest, abdomen, and pelvis. Patients who were diagnosed after 2006 could also undergo additional positron emission tomography combined with computed tomography (PET-CT). Bone marrow aspiration was performed for the exclusion of bone marrow involvement.

Patients were staged according to the Cotswold modification of Ann Arbor Staging (AAS). Bulky disease was defined as the longest diameter of a lymph node (LN) > 6 cm or a mediastinal mass with more than one-third of the maximal thoracic diameter. B symptoms were defined as unexplained fever > 38°C, unexplained weight loss > 10% within the last 6 months, and/or night sweats.

We classified the risk of the patients based on their initial stage, the presence of bulky disease, and the presence of B symptoms. The low-risk group was defined as AAS I–II without adverse factors (B symptoms or bulky disease). The intermediate-risk group was defined as AAS I–II with adverse factors or AAS III without adverse factors. The high-risk group was AAS III–IV with adverse factors. The details of the patient classification and risk-stratification are described in Fig. 1.

All patients received chemotherapy before RT. The chemotherapy regimens varied by their risk classification. The majority of the patients received chemotherapy based on the Children’s Oncology Group (COG) protocols with risk-adapted therapy [8-10,12]. Patients diagnosed before the development of the COG protocols received ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine) based regimens, which originated from studies of adult Hodgkin lymphoma. We assessed the disease response after completion of the chemotherapy as a 1st response or after the number of cycles that each protocol specified.

Patients received RT within 1 month after the completion of chemotherapy. We delineated the target volumes based on the guidelines for IFRT and INRT [13,14]. Gross target volume (GTV) was defined as visibly involved LNs based on the pre- and post-chemotherapy PET-CT. For IFRT, clinical target volume (CTV) covered the main involved lymph node region in the pre-treatment CT or PET-CT. For INRT, we considered the initial volume of the involved LNs or residual involved LNs on post-treatment PET-CT to contour the CTV. We contoured the planning target volume (PTV) by extending 7–10 mm from the CTV, considering organ movements and set-up variations. We delivered 19.8–36 Gy to the PTV with a fraction size of 1.5–2.0 Gy. In particular, patients with a complete remission (CR) at the 1st response received RT with a dose less than 30.6 Gy. After the results from the COG protocols for pediatrics and young adults were published, our institution further decreased the dose for CR patients to 25.2 Gy [8,10]. Patients who did not achieve a CR at the 1st response received boost RT to the residual involved LN. Overall, we mostly delivered a total RT dose under 40 Gy.

Fig. 1. Flow chart with selection criteria and risk-stratification. pHL, pediatric Hodgkin lymphoma; CMT, combined modality treatment; AMC, Asan Medical Center; COG, Children’s Oncology Group.
After completion of CMT, we performed a physical examination; neck, chest, and abdominopelvic CT and/or PET-CT as the final response assessment. Non-complete responders (non-CR) subsequently received additional treatment. Regular follow-ups with whole-body CT or MRI were performed every 6 months until 2 years after the completion of treatment, and every 1 year after that. A CR was defined as a more than 70% decrease of the sum of the products of the perpendicular diameters of measurable lesions (SPPD) for the patients with CT only [8]. For the patients with PET-CT, a CR was defined as Deauville Criteria 1 to 3 [15]. A partial response (PR) was defined as a decrease of SPPD between 50%-70% for CT only, and Deauville Criteria 4 without any new lesions. Acute and late toxicities were evaluated based on the pre- and post-treatment general blood chemistry, thyroid function test, post-treatment imaging, pulmonary function tests, echocardiograms, and systemic review. We evaluated acute toxicities during treatment and the 1 month after completion of CMT. Acute toxicities were divided into chemotherapy-induced and RT-induced toxicities. Thyroid function and pulmonary function tests were conducted for patients who received RT to these organs or by the clinician’s decision. Patients with a high cumulative anthracycline dose underwent an echocardiogram at least once after the CMT. We evaluated the severity of the toxicities with the Common Terminology Criteria for Adverse Events version v4.03 [16].

We used the Kaplan-Meier method for survival analysis with SPSS software for Windows (version 22.0; IBM, Armonk, NY, USA). OS was defined as the time from the start of the combined therapy to any cause of death. EFS was defined as the time from the start of the combined therapy to the progression or relapse of the disease, or the occurrence of a secondary malignancy.

Results

1. Patient characteristics
A total of 27 pediatric patients who received CMT for pHL were analyzed (Table 1). The median age at diagnosis was 14 years (range, 4 to 19 years). The male to female ratio was 1.7:1. The majority of patients had only supradiaphragmatic involvement (n = 22; 81.5%). Cervical lymphadenopathy was the most frequently involved region (n = 25; 92.6%), followed by mediastinal lymphadenopathy (n = 16; 59.3%).

Histopathologic subtypes were classified as follows: nodular sclerosis (17), mixed cellularity (6), lymphocyte predominant (3), and not specified (1). B symptoms were observed in only 4 patients, and 3 of them had night sweats while 1 had unexplained fever. Seven patients had bulky disease (25.9%). A total of 6 patients had extranodal involvement: spleen (4) and lung (2).

We stratified patients based on the COG risk-stratification protocol. Fourteen patients were low-risk, 11 patients were intermediate, and 2 patients were high-risk. Patients were treated based on the risk-adapted chemotherapy regimens.

2. Treatment and response
We assessed the response to chemotherapy by the initial staging method, CT, or PET-CT. PET-CT was applied after 2006, and only 8 patients (29.6%) underwent PET-CT. Thirteen patients were considered to have a CR (48.1%) at the 1st response. Only one patient had progressive disease. Within the patients who underwent PET-CT, 4 patients were considered to have a CR (50%) at the 1st response.

After the completion of chemotherapy, all 27 patients received IFRT or INRT. Among these patients, 14, 12, and 1 received 2D, 3D, and intensity-modulated radiotherapy (IMRT), respectively. A comparison of the 2D/3D-conformal radiotherapy (CRT) and the IMRT is presented in Fig. 2. The median RT dose was 25.2 Gy (range, 19.8 to 200 Gy).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>14 (4–19)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>Ann Arbor Staging</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>II</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>III</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Lymphocyte predominant</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Not otherwise specified</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>25 (92.6)</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>Axilla</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>B symptoms</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>No</td>
<td>23 (85.2)</td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>No</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>No</td>
<td>21 (77.8)</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).
The median fraction size was 1.8 Gy/fraction (range, 1.5 to 2.0 Gy/fraction). Based on the response to the chemotherapy, the prescribed RT dose was different. For the 18 CR patients, the median RT dose was 25.2 Gy (range, 19.8 to 41.2 Gy). Nine non-CR patients received additional RT to the residual LNs. The median RT dose of the non-CR groups was 35.6 Gy (range, 25.2 to 40.6 Gy). The total RT dose of the non-CR group was significantly higher (p < 0.001).

A CR was achieved in 23 patients after CMT (85.2%). Five patients achieved a CR out of 6 patients with subsequent PET-CT. Five patients received additional chemotherapy: 3 cases with a PR and 1 case with continuous progression. One patient achieved a CR based on PET-CT, but was suspicious for residual disease on enhanced CT, so additional chemotherapy was prescribed. Except for the patient with progressive disease, 3 patients with a PR after CMT achieved a CR after additional chemotherapy. A summary of the CMT of each patient is presented in Table 2.

### 3. Oncologic outcomes

The median follow-up period of the patient group was 125 months (range, 9 to 337 months). The 10-year EFS and OS were 88.9% and 96.3%, respectively (Fig. 3).

Only 2 patients had relapsed or progressive disease after CMT. The patient with progressive non-responsive disease mainly progressed in the mediastinum with tracheal obstruction, so this patient first received boost RT of 20 Gy to the mediastinal bulky mass and subsequently received IFRT that targeted the residual LNs. This patient subsequently received ESHAP (etoposide, solumedrol, ara-C, cisplatin) and two cycles of DICE (dexamethasone, ifosfamide, cisplatin, etoposide) but died of disease progression.

The patient with relapsed mediastinal disease presented with extensive LN involvement throughout the neck, upper and lower mediastinum, and spleen involvement. This patient received 30 Gy of INRT targeting the neck and upper mediastinum. A relapse occurred out-of-field in the mediastinum slightly above the diaphragm. This patient subsequently received high-dose slow early response DECA (dexamethasone, etoposide, cisplatin and cytarabine) chemotherapy supported by peripheral blood stem cell transplantation and regained a CR status.

### 4. Toxicities and secondary malignant neoplasms

Acute toxicities were mainly hematologic toxicity due to the che-
### Table 2. Summary of combined modality treatment of pediatric Hodgkin lymphoma patients

<table>
<thead>
<tr>
<th>Patient#</th>
<th>Diagnosis year</th>
<th>Risk group</th>
<th>Chemotherapy (cycle)</th>
<th>RT dose (Gy)</th>
<th>RT method</th>
<th>Response</th>
<th>Event</th>
<th>Status at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1990</td>
<td>Low</td>
<td>ABVD/MOPP (6)</td>
<td>19.8</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 337 mo</td>
</tr>
<tr>
<td>2</td>
<td>1991</td>
<td>Low</td>
<td>MOPP (8)</td>
<td>19.8</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 330 mo</td>
</tr>
<tr>
<td>3</td>
<td>1993</td>
<td>Low</td>
<td>MOPP+COPP (8)</td>
<td>30.6</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 65 mo</td>
</tr>
<tr>
<td>4</td>
<td>1995</td>
<td>Low</td>
<td>COPP (4)</td>
<td>23.4</td>
<td>2D</td>
<td>CR</td>
<td>Thyroid cancer, 7.2 yr</td>
<td>CR at 280 mo</td>
</tr>
<tr>
<td>5</td>
<td>1998</td>
<td>Low</td>
<td>ABVD (6)</td>
<td>28</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 96 mo</td>
</tr>
<tr>
<td>6</td>
<td>1998</td>
<td>Low</td>
<td>ABV/COPP (4)</td>
<td>25.2</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 55 mo</td>
</tr>
<tr>
<td>7</td>
<td>2000</td>
<td>Low</td>
<td>DBVE (2)</td>
<td>25.2</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 88 mo</td>
</tr>
<tr>
<td>8</td>
<td>2000</td>
<td>Low</td>
<td>ABV/COPP (4)</td>
<td>35.2</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 207 mo</td>
</tr>
<tr>
<td>9</td>
<td>2002</td>
<td>Low</td>
<td>DBVE (6)</td>
<td>25.2</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 218 mo</td>
</tr>
<tr>
<td>10</td>
<td>2002</td>
<td>Low</td>
<td>ABV (6)</td>
<td>25.5</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 136 mo</td>
</tr>
<tr>
<td>11</td>
<td>2003</td>
<td>Low</td>
<td>DBVE (4)</td>
<td>25.2</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 127 mo</td>
</tr>
<tr>
<td>12</td>
<td>2004</td>
<td>Low</td>
<td>DBVE (4)</td>
<td>36</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 156 mo</td>
</tr>
<tr>
<td>13</td>
<td>2005</td>
<td>Low</td>
<td>DBVE (4)</td>
<td>36</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 123 mo</td>
</tr>
<tr>
<td>14</td>
<td>2006</td>
<td>Low</td>
<td>DBVE (4)</td>
<td>40.6</td>
<td>3D</td>
<td>PR</td>
<td>-</td>
<td>CR at 113 mo</td>
</tr>
<tr>
<td>15</td>
<td>2007</td>
<td>Low</td>
<td>AVPC (4)</td>
<td>41.2</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 157 mo</td>
</tr>
<tr>
<td>16</td>
<td>1997</td>
<td>Intermediate</td>
<td>MOPP (4)</td>
<td>30.6</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 257 mo</td>
</tr>
<tr>
<td>17</td>
<td>1998</td>
<td>Intermediate</td>
<td>ABV/EDAP (10)</td>
<td>39.6</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 211 mo</td>
</tr>
<tr>
<td>18</td>
<td>2004</td>
<td>Intermediate</td>
<td>ABVD (6)</td>
<td>25.2</td>
<td>2D</td>
<td>CR</td>
<td>-</td>
<td>CR at 151 mo</td>
</tr>
<tr>
<td>19</td>
<td>2006</td>
<td>Intermediate</td>
<td>ABVE-PC (6)</td>
<td>40</td>
<td>3D</td>
<td>PR</td>
<td>-</td>
<td>CR at 125 mo</td>
</tr>
<tr>
<td>20</td>
<td>2006</td>
<td>Intermediate</td>
<td>ABVD (4)</td>
<td>30.6</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 58 mo</td>
</tr>
<tr>
<td>21</td>
<td>2009</td>
<td>Intermediate</td>
<td>ABVE-PC (4)</td>
<td>30</td>
<td>3D</td>
<td>PR</td>
<td>-</td>
<td>CR at 89 mo</td>
</tr>
<tr>
<td>22</td>
<td>2011</td>
<td>Intermediate</td>
<td>ABVE-PC (4)</td>
<td>30</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 105 mo</td>
</tr>
<tr>
<td>23</td>
<td>2012</td>
<td>Intermediate</td>
<td>ABVD (3)</td>
<td>36.2</td>
<td>3D</td>
<td>PD</td>
<td>Died of disease progression</td>
<td>Died at 9 mo</td>
</tr>
<tr>
<td>24</td>
<td>2016</td>
<td>Intermediate</td>
<td>ABVE-PC (6)</td>
<td>25.2</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 37 mo</td>
</tr>
<tr>
<td>25</td>
<td>2017</td>
<td>Intermediate</td>
<td>ABVE-PC (6)</td>
<td>30</td>
<td>IMRT</td>
<td>CR</td>
<td>Mediastinal relapse</td>
<td>CR at 34 mo</td>
</tr>
<tr>
<td>26</td>
<td>2005</td>
<td>High</td>
<td>DBVE (4)</td>
<td>36</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 151 mo</td>
</tr>
<tr>
<td>27</td>
<td>2015</td>
<td>High</td>
<td>ABVE-PC (5)</td>
<td>21</td>
<td>3D</td>
<td>CR</td>
<td>-</td>
<td>CR at 58 mo</td>
</tr>
</tbody>
</table>

RT, radiotherapy; CR, complete response; PR, partial response; PD, progressive disease; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; MOPP, nitrogen mustard, vincristine, prednisone, and procarbazine; ABV/COPP, doxorubicin, bleomycin, and vinblastine/cyclophosphamide, vincristine, procarbazine, and prednisone; EDAP, etoposide, dexamethasone, cytarabine, and cisplatin; DBVE, doxorubicin, bleomycin, vincristine, and etoposide; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide.

Fig. 3. Kaplan-Meier curves for (A) event-free survival and (B) overall survival in patients with pediatric Hodgkin lymphoma.
motherapy. Severe neutropenia (Grade ≥ 3) occurred in 18 patients. We observed 8 patients with febrile neutropenia during chemotherapy that required admission and treatment with intravenous antibiotics. Severe thrombocytopenia and anemia were recorded in 6 and 2 patients, respectively.

There was no severe non-hematologic RT-induced toxicity observed. Grade II esophagitis and cough were observed in only one patient each. High dose RT did not show a higher incidence of RT-induced toxicity. We did not observe any long-term sequelae from severe acute toxicity. Details of the acute toxicities are described in Table 3.

The median follow-up period for the surviving patients was 126 months (range, 34 to 337 months). We performed echocardiograms in 10 out of 26 survivors (38.5%) after completion of the CMT. There was no abnormal echocardiogram observed.

Of the 13 patients who underwent a pulmonary function test before the treatment, 8 patients received a follow-up pulmonary function test after completion of the treatment. Only one patient had a mild obstructive pattern, with a decreased forced volume capacity and an FEV1 of 1.68 L (68% predicted) and 1.68 L (73% predicted), respectively. This patient received 4 cycles of ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) and 30 Gy of RT to the mediastinum.

Thyroid function test were conducted in 12 patients (44.4%) among 23 patients with neck irradiation. Thyroid hormone-replacement therapy was required in 7 patients (58.3%) who underwent thyroid testing. All patients with hormonal replacement had received RT to the neck. The median RT dose of the patients with thyroid-hormone replacement was 30 Gy (range, 19.8 to 41.2 Gy), whereas that of the patients without thyroid toxicity was 30.3 Gy (range, 19.8 to 40.6 Gy). Also, RT techniques did not differ between the two groups.

We observed only one secondary malignant neoplasm (SMN) during the follow-up period. One patient experienced a non-hematologic secondary malignancy, a papillary thyroid cancer that was diagnosed 7.2 years after 23.4 Gy of neck irradiation. There were no secondary hematologic malignancies observed.

**Discussion and Conclusion**

Pediatric Hodgkin lymphoma is a curable disease with an extremely low incidence in childhood and adolescence. pHL shows a bimodal age-specific distribution and it is the third most common pediatric malignancy in the United States [2]. Long-term OS and EFS of pHL exceeds 90% in western reports regardless of the treatment method [3].

The clinicopathology of HL is different among different ethnic groups [4]. A lower incidence is observed in Asia compared with North America and Australia. Studies conducted in India showed a male predominance, a younger age at presentation, and an increased incidence of a mixed cellularity subtype than in western reports [17]. Hwang et al. [11] reported a change in the pathologic pattern from mixed cellularity predominance to nodular sclerosis predominance. We also observed a similar pattern of pHL with a male (63%) and nodular sclerosis subtype predominance. Kobayashi et al. [18] also reported a male predominance and a low incidence of 20–30 patients per year in Japan. Park et al. [1] reported that the crude incidence was 1.3 per million among those 0 to 14 years of age, and did not observe a bimodal increase during childhood and adolescence in Korea. Also, the majority of patients were over 10 years old at the time of diagnosis (crude incidence: 10–14 years, 2.4 vs. 0–9 years, 1.3). Similarly, only 6 patients (22%) were under 10 years old at the time of diagnosis.

**Table 3. Acute toxicity after combined modality treatment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chemotherapy-induced toxicity</th>
<th>Radiation-induced toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Toxicities were assessed by the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.
10 years old in our study.

Even though there are discrepancies in the clinical characteristics between western and Asian countries, long-term survival and EFS are comparable (Table 4). In this study, long-term survival was comparable with other prospective studies, with 10-year OS and EFS of 96.3% and 89.3%, respectively. However, patients in our study received heterogeneous treatment because of the long duration of the case collection period and the development of the risk-based chemotherapy regimen.

For the low-risk group, prospective studies have reported an excellent survival with low-dose IFRT [9,10,19]. There is controversy about the necessity of RT for patients with a good response after initial chemotherapy, with concerns about balancing disease control with the risk of long-term toxicities. In the CCG 5942 trial [10], patients received ABV/COPP (doxorubicin, bleomycin, and vinblastine/cyclophosphamide, vincristine, procarbazine, and prednisone) chemotherapy.

After the chemotherapy, patients with a CR were randomly assigned to 21 Gy IFRT or no RT. The 10-year EFS was significantly improved (100% vs. 89.1%) in response to the IFRT, whereas no benefit for survival was observed (97.1% vs. 95.9%). However, the POG 8625 trial [20], a randomized study of 25.5 Gy of RT or additional chemotherapy, did not report any difference in EFS or OS (EFS, 91.1% vs. 82.6%; OS, 96.8% vs. 93.6%). In the current study, there were no relapses or treatment failures in the low-risk group (n = 15), but we did observe one case of SMN that was diagnosed 7.2 years after treatment. The median RT dose was 25.5 Gy (range, 19.8 to 41.2 Gy) in the low-risk group. Dose or field reduction of RT in low-risk groups to reduce over-treatment or long-term toxicities may be considered due to the excellent disease control observed in the current study and in other prospective study results.

Prospective trials for intermediate to high-risk patients reported EFS between 84% to 94% [8,10,21,22]. In our study, 10-year OS and EFS were 91.7% and 83.3%, respectively. We observed one treatment failure and one mediastinal relapse. Both patients did not achieve a CR at the 1st response. No patients with a CR after chemotherapy experienced a relapse. In the CCG 5942 trial [10], the EFS in the intermediate to high-risk groups who achieved a CR after chemotherapy was not significantly improved after IFRT (intermediate, 84.0% vs. 78.0%; high, 88.5% vs. 79.9%). However, the authors did not conclude that RT was detrimental to these groups due to the small size of the groups and their need for more aggressive chemotherapy. As indicated above, RT in intermediate to high-risk patients shows mixed data, especially for patients with a CR after chemotherapy. Additional studies are needed to identify the optimal RT field and dose for patients who achieve a CR after chemotherapy.

As the CMT of pHL guarantees extremely high rates of long-term survival, there have been increasing problems with serious long-term toxicities among long-term survivors, including cardiac, pulmonary, and endocrinical complications. We observed the surviving patients after a median follow-up of 126 months (range, 34 to 337 months). Because of the retrospective nature of our study, we could not obtain full imaging and chemistry work-ups for complete observations of late toxicity.

Tukenova et al. [23] reported that cumulative RT dose and anthracycline usage were associated with an increased risk of late mortality. It is known that cardiac late-toxicity is related to the cumulative anthracycline dose, and it may occur as long as 10 years after completion of therapy with a low cumulative anthracycline dose [24]. Most of our patients received anthracycline-based chemotherapy, and among these patients, we performed echocardiogram for 10. We did not observe any late cardiovascular toxicity even with long-term follow-up.

Thyroid dysfunctions are the most common late toxicities, including hypothyroidism, hyperthyroidism, and secondary thyroid

### Table 4. Treatment outcomes of prospective trials and current study

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk group</th>
<th>Number of patients</th>
<th>Chemotherapy</th>
<th>Radiation dose (Gy)</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG 5942</td>
<td>All</td>
<td>826</td>
<td>4–6 COPP/ABV</td>
<td>21</td>
<td>83.5 (10-yr)</td>
</tr>
<tr>
<td>POG 9426</td>
<td>Low</td>
<td>255</td>
<td>2–4 ABVE</td>
<td>25.5</td>
<td>88.3 (5-yr)</td>
</tr>
<tr>
<td>AHOD 0431</td>
<td>Low</td>
<td>175</td>
<td>CR: No-RT</td>
<td></td>
<td>77.5 (4-yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR/SD: 21</td>
<td></td>
<td>82.8</td>
</tr>
<tr>
<td>AHOD 0031</td>
<td>Intermediate-high</td>
<td>382</td>
<td>4–6 ABVE-PC</td>
<td>RER; CR: No-RT</td>
<td>86.7 (4-yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RER; CR: 21</td>
<td>87.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>305</td>
<td></td>
<td>SER: 21</td>
<td>77.4</td>
</tr>
<tr>
<td>POG 9425</td>
<td>High</td>
<td>216</td>
<td>3–5 ABVE-PC</td>
<td>21</td>
<td>84.0 (5-yr)</td>
</tr>
<tr>
<td>Current study</td>
<td>All</td>
<td>27</td>
<td>Heterogeneous</td>
<td>19.8–41.2</td>
<td>88.9 (10-yr)</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; PD, progressive disease; RT, radiotherapy; EFS, event-free survival; RER, rapid early response; SER, slow early response; COPP/ABV, cyclophosphamide, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide.
cancer. Sklar et al. [25] reported that 34% of patients were diagnosed with at least one type of thyroid dysfunction, and hypothyroidism was the most common dysfunction. The risk for thyroid dysfunction is 4–5 times higher after neck irradiation. Hancock et al. [26] observed 50% of patients had 20-year long-term thyroid toxicity after mantle-field RT. The RT dose to the thyroid gland is also an important factor for thyroid dysfunction. Thyroid V30 is an independent predictor of hypothyroidism. In patients with thyroid V30 > 62.5%, the incidence of hypothyroidism is significantly increased (high-volume 70.8% vs. low-volume 11.5%; p < 0.01) [27]. Even though we observed a similar incidence as in previous studies with larger field RT, the actual proportion of thyroid toxicities in our group may be lower because only half of the patients underwent thyroid function test. Additional dose-sparing for the thyroid by block or conformal therapy is needed to decrease long-term thyroid toxicity further.

SMN is associated with the RT dose and the use of alkylating agents or anthracyclines [28,29]. Common SMNs are leukemia, sarcoma, thyroid, and breast cancers. However, the incidence of SMN does not change linearly in response to the RT dose or field. The risk of thyroid cancer is the highest at 20 Gy, and then it decreases as the RT dose increases [30]. We observed a patient with papillary thyroid cancer who received 23.4 Gy neck irradiation, which is consistent with previous reports. We did not observe any SMNs after higher irradiation doses.

There are several limitations to our current study. First, we analyzed a small number of patients over 30 years. Due to the small number of patients and the high disease control rate, we could not evaluate the prognostic factors for pHL. Moreover, the patients received heterogeneous chemotherapy based on risk-grouping. The current study included all risk groups and included some patients who were diagnosed before the development of specific chemotherapy regimens for children, which led to the use of diverse chemotherapy regimens. Thus, it is hard to determine the necessity of RT or to evaluate long-term toxicities in this patient group. In addition, the RT technique and protocols have evolved over the last 30 years, and thus the patients received heterogeneous RT techniques, including 2D, 3D-CRT, and IMRT. However, this study has a strength in that the same medical team used consistent decision criteria, and there were a relatively large number of cases, despite the low incidence of pHL in Korea. Thus, there was some homogeneity of treatment provided by the same medical team. The current study has clinical meaning because it only assessed survival and long-term toxicity after CMT with IFRT or INRT for pHL. Further investigation with multicenter, large-scale studies is needed to optimize the treatment with lower toxicity, but the findings of the current study strengthen the evidence base supporting CMT with a smaller RT field in Korea.

In conclusion, CMT with IFRT and INRT may lead to favorable long-term survival. Smaller field RT could be considered as an adaptive treatment option with lesser long-term toxicities as compared with high-dose, large-field RT.

Conflict of Interest

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

References

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Total marrow and lymphoid irradiation with helical tomotherapy: a practical implementation report

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Introduction

The total body irradiation (TBI) with extended source-to-skin distance (SSD) is a simple and robust technique to deliver myeloablative treatment as part of the conditioning regimen for allogeneic bone marrow transplant (ABMT) for myeloid and lymphoid leukemia. However, this modality does not spare organs-at-risk (OAR) except lungs and results in large heterogeneities in radiation dosage across the body. Total marrow irradiation (TMI) targets the entire skeleton and lymphoid tissues while sparing the organs at risk such as parotids, oral cavity, lens, thyroid, lungs, heart, bowel, kidneys, liver, breast, etc., and is emerging as an alternative to TBI as it has shown reasonable safety and efficacy in phase I/II trials [1–6]. Addition of lymphoid irradiation to TMI which amounts to total

Keywords: Total body irradiation, Lymphoid irradiation, Stem cell transplantation, Hematopoietic, Helical tomotherapy, Resource allocations
marrow and lymphoid irradiation (TMLI) has the potential to reduce the rejection against the lymphocytes in donor marrow. Currently several groups are evaluating its role in standard and high-risk acute leukemia [7]. TMLI also enables the possibility of dose escalation which has been shown to reduce the rate of recurrences [8] and hence is an attractive treatment option for patients at higher risk of treatment failures.

Although a few groups have published the technique and clinical results of TMLI, there is a significant variation among the published series on various aspects of immobilization, target delineation including margin recipe, treatment optimization, plan evaluation and treatment delivery. Apart from these variations, the process of TMLI itself is laborious and time intensive which makes adoption of this technique a formidable challenge.

Based on available human and technical resources at our center, we have attempted to standardize the methodology of TMLI; analyze the resource and time requirements to accomplish this; and evaluate our initial experience including dosimetry, patient specific quality assurance and patient set-up parameters using helical TomoTherapy (Accuray Inc., Sunnyvale, CA, USA) at our center.

**Materials and Methods**

Patients were considered for this procedure after due discussions in the multi-disciplinary tumor board in close coordination with the hemato-oncology team. Feasibility for TMLI in these patients was based on the ability and willingness to lie down on the treatment couch for at least 1.5 hours. All patients signed an informed consent document before the procedure. Our experience of treating the first five consecutive adult patients (age > 18 years) has been used in this practical implementation report.

1. **Simulation**

Simulation was done after the insertion of all catheters or venous access as deemed fit by the hemato-oncology team. Patients were positioned supine in a whole-body vacuum bag encompassing the entire body in a neutral position and a 5-clamp thermoplastic mask on a standard neck support was made to immobilize the head and shoulder (Fig. 1A, 1B). The arm, forearm and hands were placed closely touching the lateral aspect of the body. The knees were placed in a comfortable position and the height was adjusted on the vacuum bag. In males, the scrotum was strapped to the lower abdomen and marked. The firm impression of heel and toes on the vacuum bag was captured. Before acquiring computed tomography (CT) imaging, a thin copper wire was placed over the mid-thigh bilaterally. Lines were drawn horizontally over upper and lower limbs with corresponding lines over the vacuum bag to aid reproducibility (Fig. 1C).

As helical TomoTherapy unit can treat till a maximum length of 135 cm, two sets of CT scans (Aquilion LB; Toshiba, Tokyo, Japan) of 5-mm slice thickness in free-breathing were acquired for each patient. The first scan was acquired from vertex to distal thigh (at least 5 cm beyond the wire placed over mid-thigh) in the head first supine (HFS) position. Then the patient along with the immobilization was rotated by 180° and a second CT scan was acquired from toes (entire vacuum bag to be included) to the upper thigh (at least 5 cm beyond the wire placed over mid-thigh) in feet first supine (FFS) position. Both scans encompassed the entire thigh to aid in registration for the evaluation of the summated plan. For the FFS scan the CT reference point was marked over the chin and for the FFS scan over the knee.

2. **Target delineation**

CT images were transferred to RayStation treatment planning sys-
tem V7.0 (RaySearch Laboratories, Stockholm, Sweden), which is the preferred system for target delineation in our department. Clinical target volume (CTV) included entire bony skeleton, brain, testes, spleen and major lymphatics. CTV defined on HFS and FFS scan included bones auto-segmented based on grey level (Hounsfield units [HU]) thresholding ranging between 250–1700 HU and edited appropriately. Bony CTV was split into multiple segments (skull, chest, upper/lower limbs, vertebra, and pelvis) to enable differential planning target volume (PTV) margins. Mandible, hyoid bone, patella, and larynx were excluded from CTV. Isotropic PTV margin of 3 mm, 5 mm, 7 mm, 10 mm, and 5 mm were given to CTV skull, vertebra, chest/spleen, upper limb (and lower limb for FFS scan), and pelvis (and scrotum), respectively. For patients with maximum lateral separation exceeding 45 cm, an additional margin was created for PTV upper limbs since the field-of-view of megavoltage CT (MVCT) was limited to 40 cm.

Lymphatics delineated included cervical, supraclavicular, mediastinal, axillary, entire para-aortic chain, external and internal iliac, andinguinal nodes (Fig. 2). A uniform PTV margin of 5 mm was applied to generate lymph nodal PTV. Individual PTV’s generated were summated to create PTV. OAR delineated were eyes, lens, midline mucosa (oral, pharyngeal, laryngeal, tracheal and esophageal mucosa), lungs, heart, liver, bowel, kidneys, parotids, thyroid, breast, and ovaries. The primary planning goals were to ensure 98% of CTV to receive 11.4 Gy (95% of 12 Gy) with D2% of CTV not exceeding 13.2 Gy (110% of 12 Gy), Lung D50 not exceeding 8.5 Gy and no volume of OAR receiving > 12.6 Gy (105% of 12 Gy).

3. Treatment planning, plan evaluation and patient-specific quality assurance (PSQA)

We used the Precision planning system (iDMS version 1.1.1.1; Accuray Inc.) for optimization and dose calculation purposes for treatment delivery on Radixact X9 tomotherapy system (Accuray Inc.). For optimization, the entire target volume in HFS and FFS images series was divided into three parts, namely PTV-upper, PTV-lower, and PTV-Junction. The length of the junction was 10 cm (between the upper thigh and the knee) and it was divided into five sub-volumes in each CT image series to create a dose gradient. They were labeled as PhyUG2Gy, PhyUG4Gy, PhyUG6Gy, PhyUG8Gy, PhyUG10Gy, PhyLG2Gy, PhyLG4Gy, PhyLG6Gy, PhyLG8Gy, and PhyLG10Gy. The copper wires placed on the left and right mid-thigh were used as common reference markers to correlate the axial positions from both HFS and FFS CT image series. Using this common reference marker, the extension and location of the three PTV’s were verified in both the CT image series.

As a standard protocol CT tabletop in the image series was replaced by the Radixact couch model. The patient position was set using a green laser in such a way that the entire body was fit within the field of view. Two separate treatment plans were generated on each of the scans (HFS and FFS) to cover the entire target with a complementary dose gradient across the junction (Fig. 3A, 3B).

Plan setup parameters were chosen to meet the clinical goals of the target. Pitch from 0.3 to 0.43, field width of 5 cm, modulation factor of 2.5–3.5 for HFS orientation and 2.15–2.5 for FFS were used. A higher heterogeneity was accepted near the upper limbs especially near the forearm and hands. Pitch values were optimized to have minimal thread effect and good target coverage. Higher modulation factors were used for initial iterations and subsequently modified to have efficient beam delivery time.

For summation of the plans generated on HFS and FFS CT’s, RayStation treatment planning system (TPS) was used due to limitation in summating plans generated on two differently referenced CT’s on Precision TPS. Deformable image registration (DIR) of both these CT’s were performed using anatomically constrained deformation algorithm (ANAConDA) on RayStation, manually verified and edited if required. Using the anatomical map from DIR the dose on the FFS CT series was deformed onto the HFS CT series. The dose grids

Fig. 2. Delineated lymphatic chains (cervical, red color; axillary, purple; cobalt blue, mediastinal up to hilar; light cobalt blue, para-aortic lymph node; pelvic lymph nodal chains, green).

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From the each of the plans were summated on HFS CT series and the dose profile across the junction (Fig. 4) was evaluated.

As part of the PSQA, we measured the dose using a cylindrical cheese phantom (Accuray Inc.) with the A1SL Ion Chamber (Standard Imaging Inc., Middleton, WI, USA) and dose map using ArcCHECK helical diode array detector (Sun Nuclear, Melbourne, FL, USA). Since the target volume exceeded 120 cm, multiple point doses (3 for HFS plan and 2 for FFS plan) were measured to cover the entire target. Each point dose measurement was associated with a specific quality assurance plan. Before each measurement phantom position was verified using MVCT image registration with planning CT. The measured dose maps were compared with the dose from TPS and evaluated using gamma criteria of 3% dose difference and 3 mm distance to agreement. The mean gamma pass-
ing rate was 97.82% (96.4%-99%) which was above our acceptance limit (≥ 95%).

4. Treatment delivery and in vivo dosimetry
Pre-treatment imaging and treatment delivery were divided as the patient was treated in both HFS and FFS positions as described in the pictogram (Fig. 5). Treatment was interrupted each time after a pre-specified time for image verification. In HFS treatment, the first MVCT scan was obtained from lower neck to upper abdomen level to correct any significant longitudinal and yaw errors manually. The second MVCT was acquired from the vertex to the mid-chest level. After applying the necessary lateral and vertical corrections, patient was treated up to the upper abdomen. The third MVCT scan was obtained encompassing the entire abdomen up to mid-thigh, the position of scrotum was verified, and the rest of the patient treatment was completed for HFS plan. Subsequently, the patient was rotated by 180° (in yaw plane) with the same immobilization and alignment in place for FFS treatment plan. The fourth MVCT was acquired from ankle to thigh, couch corrections were applied (including the longitudinal corrections since the patient was moved manually) and treatment was delivered with FFS plan. After couch corrections, before the delivery of treatment, dose-wash from the treatment plan were over-laid and manually verified for PTV to be covered by 95% dose-wash. The dosimetric accuracy of the junction was verified using GafChromic EBT3 film placed over the junction.

Results
Five patients (3 males and 2 females) with a median age of 36 years (range, 25 to 49 years) underwent this procedure from the 7th–5th day before ABMT. The median patient height was 167 cm (range, 160 to 178 cm). All patients received 2 daily fractions of 2 Gy each for 3 days with a minimum gap of 8 hours between each fraction. The mean beam-on-time per fraction was 33.25 minutes with a dose rate of 1051 MU/minute. The resources and time requirements for the treatment planning and delivery procedure have been summarized in Table 1.

The desired target coverage and OAR sparing was satisfactorily

Table 1. Time, resource requirements for the TMLI (as per local practice)

<table>
<thead>
<tr>
<th>Process</th>
<th>Median time (hr)</th>
<th>Resource</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation and image acquisition</td>
<td>1.50</td>
<td>2 Radiation therapists (verified by medical physicist and radiation oncologist)</td>
</tr>
<tr>
<td>Target delineation</td>
<td>6</td>
<td>1 Radiation oncologist</td>
</tr>
<tr>
<td>Optimization and dose calculation</td>
<td>44 (effective working hours spent by physicist = 12)</td>
<td>Medical physicist</td>
</tr>
<tr>
<td>Plan evaluation</td>
<td>1</td>
<td>1-hour verification by second medical physicist (partially shared time with other activities)</td>
</tr>
<tr>
<td>Patient specific quality assurance</td>
<td>1.50</td>
<td>Medical physicist and radiation oncologist</td>
</tr>
<tr>
<td>Treatment delivery fraction_1</td>
<td>1.75</td>
<td>2 Medical physicists</td>
</tr>
<tr>
<td>Treatment delivery subsequent fractions (5#) and in vivo dosimetry</td>
<td>1.50</td>
<td>2 Radiation therapists (verified by medical physicist and radiation oncologist)</td>
</tr>
<tr>
<td>Summary of person hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapist</td>
<td>21.50</td>
<td></td>
</tr>
<tr>
<td>Medical physicist</td>
<td>26.75</td>
<td></td>
</tr>
<tr>
<td>Radiation oncologist</td>
<td>16.25</td>
<td></td>
</tr>
<tr>
<td>In-room time for all fractions</td>
<td>9.25 per patient¹</td>
<td></td>
</tr>
</tbody>
</table>

TMLI, total marrow and lymphoid irradiation.

¹This excludes the treatment room preparation time which is about 15 minutes before each fraction.
achieved in all patients. The dose-volume parameters achieved have been summarized in Table 2. The dose homogeneity was acceptable with a mean homogeneity index (based on the International Commission on Radiation Units & Measurements [ICRU] Report 83) of 0.170 (range 0.147 to 0.190) for the combined PTV (PTV-upper + PTV-lower + PTV-junction). A higher homogeneity index (a higher inhomogeneity) was accepted only for PTV upper limbs (mean HI = 0.327, range 0.197 to 0.441). The mean of lung D\textsubscript{50}, kidney D\textsubscript{50}, heart D\textsubscript{50}, liver D\textsubscript{50}, and max dose to mucosal structures achieved were 8.15 Gy, 7.5 Gy, 8.17 Gy, 7.41 Gy, and 12.48 Gy, respectively. The liver was included in the target volume for the patient #2, which led to a higher lung D\textsubscript{50}. For the calculation of average D\textsubscript{50} for liver, this patient was excluded (Fig. 6).

Setup errors were minimal in all patients based on MVCT verification (Table 3). After manually adjusting patient position (if required) based on the first MVCT at the thoraco-abdominal level and applying the necessary couch corrections in the head neck region after the second MVCT, the subsequent imaging did not necessitate further corrections in the longitudinal axis.

The PSQA results achieved for all the patients were satisfactory as per our institutional thresholds and have been summarized in Fig. 7. On qualitative comparison of TPS calculated dose profile and measured dose profile (in vivo film dosimetry) at the same level no abnormal spikes in dose were observed in all the patients (within our threshold of +10%) (Fig. 8). All patients were successfully engrafted and are in remission at a median follow-up of 7 months.

**Table 2.** Dose volume parameters achieved (unit: Gy)

<table>
<thead>
<tr>
<th>Clinical target volume</th>
<th>Planning target volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull</td>
<td>Planning target volume</td>
</tr>
<tr>
<td>D\textsubscript{98}</td>
<td>D\textsubscript{98}</td>
</tr>
<tr>
<td>Chest</td>
<td></td>
</tr>
<tr>
<td>D\textsubscript{98}</td>
<td>D\textsubscript{98}</td>
</tr>
<tr>
<td>Trunk</td>
<td></td>
</tr>
<tr>
<td>D\textsubscript{98}</td>
<td>D\textsubscript{98}</td>
</tr>
<tr>
<td>Upper limb</td>
<td></td>
</tr>
<tr>
<td>D\textsubscript{98}</td>
<td>D\textsubscript{98}</td>
</tr>
<tr>
<td>Lower limb</td>
<td></td>
</tr>
<tr>
<td>D\textsubscript{98}</td>
<td>D\textsubscript{98}</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>11.8 ± 12.7 ± 12.7 ±</td>
<td>11.9 ± 13.0 ± 0.4 ±</td>
</tr>
<tr>
<td>0.1 ± 0.2 ± 0.1 ± 0.4 ±</td>
<td>0.5 ± 0.5 ± 0.2 ± 0.2 ±</td>
</tr>
</tbody>
</table>

**Fig. 6.** Box plot of D\textsubscript{50} and organs-at-risk (OAR) of 5 patients. Bars indicate median and interquartile range.
Fig. 7. Box plot of patient-specific quality assurance results measured by the treatment planning system (TPS) and the Phantom.

Fig. 8. In vivo junction dosimetry in a patient. (A) Sagittal view of planning computed tomography with a red arrow indicating where the film was placed on the patient for dose measurement and the region where dose profile was obtained in treatment planning system (TPS). (B) TPS measured dose profile over the specified region. (C) Dose profile obtained from Gaf-choromic film measurement over the specified region.

(range, 2.5 to 8 months).

Discussion and Conclusion

After a considerable experience with extended SSD TBI for last several years, we evaluated this methodology of TMLI, with an aim to eventually study the feasibility and safety of dose escalation in selected patients. Our objective with this study was to standardize the procedure, plan resources and time requirements and analyze our early experience with respect to dosimetry and treatment delivery.

We have demonstrated that the methodology adopted by us was safe and feasible. Certain complexities in our methodology were due to resource availability limitations. The major complexity in our
workflow was using two different planning systems to complete the treatment planning and plan evaluation. This step could be simplified by using a single planning system for the entire procedure. Another challenge in our workflow was to limit patient in-room time and hence we have standardized our image guided treatment delivery protocol to minimize repeated patient re-positioning and ensure optimal treatment efficiency.

Shinde et al. [9] compared the late toxicities with TMI/TMLI with that of TBI based on historical controls. The findings in that study showed very low incidence of radiation pneumonitis, radiation related renal toxicity, hypothyroidism, and cataract formation with TMI/TMLI compared to the historical TBI controls. The dose rate for treatment delivery in TMI/TMLI cohort was 200 cGy/min in this study (10 Gy/min in our study) which is significantly higher compared to conventional TBI dose rates which range between 5–30 cGy/min. Although, effect of dose rate on toxicities have been noted in 1–5 cGy/min range and with single fraction, there is very little evidence of its effect on toxicity with fractionated treatments even at higher dose rates. The low incidence of late toxicities as demonstrated by Shinde et al. [9] suggest that that the higher dose rate may not measurably contribute to organ dysfunction especially in the context of significant dosimetric sparing.

Helical TomoTherapy for magno-field irradiation offers a high degree of conformity, homogeneity of target coverage dose and significant sparing of OAR with optimal treatment efficiency, without the need for multiple junctions. This is possibly the reason why several groups have extensively evaluated it for TBI and TMI/TMLI [8,10–15]. Recently volumetric modulated arc therapy (VMAT) has also been evaluated in this setting to a reasonable success [16].

Although we have used helical TomoTherapy to treat our patients, the same principles can be broadly applied for VMAT as well. The target delineation for both TMI and TMLI has been varied in literature. Exclusion of mandible, maxilla, bones in the forearm, small bones of the hands and feet from the target has been diverse [1–5]. We have included the entire skeletal system excluding mandible, hyoid, laryngeal cartilage and patella.

Similarly inclusion of nodal groups varied with some authors not explicitly mentioning the nodal groups that are intentionally irradiated [8,10–11]. We have included cervical, mediastinal, para-aortic, pelvic and inguinal nodal chains and have excluded Waldeyer’s ring and porta-hepatic nodal groups in order to limit the doses to oropharyngeal mucosa and liver/bowel respectively. There is also a discrepancy when it came to inclusion of liver, which was part of the target in some and was an OAR in a few series [8,10,11,17]. Patients will be followed up to validate the appropriateness of our approach.

The dose coverage and homogeneity met our pre-specified dose constraints except in upper limbs where the inhomogeneity exceeded our thresholds. This is expected with helical TomoTherapy delivery for peripherally located targets due to increased thread effect and limited beamlet views for this region.

Lung D50 achieved in our patients was relatively higher compared to other published series of TMLI [8,10,11,17] and this is possibly due to differences in target delineation, margins and differences in target coverage goals. Varying margins to the chest wall target have been used by investigators which were based either on geometric expansion ranging from no margin up to 10 mm [10,18] or based on chest wall motion [18]. Our coverage goal of 95% of dose to 98% of CTV was higher than the 85% set by Wong et al. [10] possibly explaining higher lung D50. However, lung D50 achieved for TMLI in our cohort was comparable to that achieved by Haraldsson et al. [18] for TMI. We intend to aggressively limit lung D50 in future, especially when we escalate the doses either by using tighter margins or by relaxing the target coverage goals in the upper chest (our current mean CTV chest D50 was 99.6%).

We have used MVCT alone as a guide for patient setup verification, which mandated diligent patient immobilization and systematic imaging protocol to minimize patient repositioning. The first MVCT (lower neck to upper abdomen) in our imaging protocol was done to manually correct any longitudinal and yaw errors before proceeding with the rest of the procedure. This step significantly reduced the magnitude of couch corrections and the need for further repositioning. Considering the large diversity in methods used for immobilization and image verification, a multi-institutional effort [19] to analyze the dosimetric precision in TMI revealed that the image verification performed using a whole body MVCT yielded lesser setup corrections and better dosimetric precision compared to partial body imaging. In our study the MVCT covered the entire body, however the imaging and treatment delivery was done in segments. Because of the relatively large PTV margins used and the minimal setup corrections achieved in our study, significant dose perturbations within the target are unlikely. We also had performed manual verification of the setup by overlaying the isodose wash on the MVCT to ensure PTV coverage by at least 95% isodose-wash before treatment delivery for each segment.

Our patient setup errors and corrections were comparable to the one published recently by Mancosu et al. [20] which compared two different immobilization systems (baseplates with and without inter-fixation). The study showed lesser setup corrections when the baseplates were inter-fixed. We have used a whole-body vacuum bag and hence did not require any inter-fixation. In our study, special attention was given to extremities and scrotal position during immobilization and daily setup to minimize the repeated image verifications. The robustness of the dose at the junction was ref-
firmed with the help of film dosimetry.

As compared to TBI, TMLI is a time and resource-intensive procedure. We observed that for one patient to be successfully treated, the department would have to allocate nearly 27 physicist-hours, 21.5 therapist-hours, and 16.25 radiation oncologist-hours (Table 1). Significantly higher person-hours and in-room time as compared to other magna-field irradiations can potentially lead to stress on work-timings for all the personnel involved especially in busy radiation oncology departments. The mean in-room time of 9.25 hours per patient over 3 days, could potentially lead to significant changes in treatment schedules for other patients. We chose weekends and public holidays to treat our patients to minimize interruptions to the department’s routine.

Our beam-on time was higher compared to that reported for TMI using helical TomoTherapy and VMAT [16], but comparable to others for TMLI using helical TomoTherapy [8,10,11,17]. Our time for target delineation, treatment planning and quality assurance was comparable to that reported by others for TBI [21]. We believe that further optimization of total in-room time can be achieved with growing experience.

Since the aim of the study was to standardize our methodology and plan resource requirements, we chose to publish this report after treating the initial 5 patients. However, the dosimetric data is limited due to the small sample size and hence we may have to optimize the target and OAR dose constraints in the future on a case to case basis. All our patients were young and had healthy lung volumes enabling us to achieve desirable lung D_{50}, however this could be challenging in patients with poor lung volumes. The robust setup and minimal couch corrections noted in our study may not be possible to achieve in more challenging patients and hence may either require a more liberal margin recipe or a compromise on dose constraints. Our average in-room time of 9.25 hours per patient may pose a significant challenge while treating pediatric patients, although the need for junction would not arise in such patients (<135 cm).

In conclusion, TMLI results in significant sparing of OAR and provides an opportunity for safe dose escalation despite being a time and resource-intensive procedure. Our comprehensive report on the detailed methodology, resource and time requirements to implement TMLI would help departments planning to commission this procedure and plan their resources. We will be using this methodology in a prospective phase II trial to study the safety and feasibility of dose escalated TMLI as part of the conditioning regimen before ABMT.

**Conflict of Interest**

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

**References**


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Name (Print) ____________________________________________

Signature ______________________________________________

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임핀지 2020년 4월 1일 보험급여 적용

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

- 급히 안정 기간은 최대 12개월로 함
- 이전 PD-1 inhibitor 등 면역관문처제 치료를 받지 않은 경우에 한함.

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

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

3-year overall survival update2

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Time from randomisation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMFINZI (n=476)</td>
<td>Probability of OS</td>
</tr>
<tr>
<td>Placebo (n=237)</td>
<td></td>
</tr>
</tbody>
</table>

1. DURVALUMAB OS rate differences compared to Placebo.
2. As of January 31, 2019 (data cutoff)
3. Probability of OS
4. 31% REDUCTION in risk of death (HR=0.69; 95% CI, 0.55-0.86)
5. MEDIAN OS NOT YET REACHED VS 25.1 m vs for placebo
6. NOTES TO EDITORS

REFERENCE 1. 보건의료 가이드 특수치료 환자의 진료관리(2020년 4월 1일 보험급여 적용).의료법 제149조의3 및 제150조의3의 개정 시행(2020년 4월 1일).

STUDY DESIGN: The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically verified advanced-stage, unresectable NSCLC, with PD-L1 expression rates of ≥ 1% in NSCLC tissue or with positive PD-L1 expression status by IHC testing in NSCLC tissue. The PACIFIC trial was a phase III, double-blind, placebo-controlled, multicentre study of IMFINZI (durvalumab) plus placebo (n=476) or placebo (n=237) for 1 year in patients with stage III non-small-cell lung cancer (NSCLC) who had undergone chemoradiotherapy (CRT) and had no evidence of disease progression, including patients with documentation of disease progression or unacceptable toxicity, or consent withdrawal. Randomisation was stratified by age of the patient (<65 years vs ≥65 years), sex, and smoking history (current or former vs never smoked). The primary and secondary endpoints were progression-free survival (PFS) as assessed by blinded independent central review and overall survival (OS), respectively.

PREScribing INFORMATION

- 난성능 뇌종양이나 약물과의 상호작용의 발생 가능성이 있다.
- IMFINZI는 스테로이드 및 비스테로이드 스테로이드 요법 용량 조절을 고려해야 한다.
- IMFINZI는 스테로이드 및 비스테로이드 스테로이드 요법 용량 조절을 고려해야 한다.

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