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Aims and Scope

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

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

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

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Localized intracranial germinoma: is it time to re-define target volume for whole ventricular irradiation?

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The treatment strategy for children with brain tumors has been to reduce the intensity of treatment by minimizing long-term toxicities, while preserving cure rates. In this context, localized intracranial germinoma is the best fit for this strategy, and attempts have been made over the last 30 years to reduce the dose and volume of radiotherapy. However, the definition of the target volume for radiotherapy is uncertain and complex and no formal guidelines exist, particularly for whole ventricular irradiation (WVI).

In this issue of Radiation Oncology Journal, the paper “Excluding prepontine cistern from whole ventricle radiotherapy target volume in localized germinoma” by Ryu and Lee [1] is very encouraging in a situation where evidence cannot be secured through systematic clinical trials. They reported that there was no relapse in the prepontine cistern and that endoscopic third ventriculostomy was not a significant prognostic factor. They further clarified that exclusion of the prepontine cistern resulted in significantly lower mean doses to the brainstem and cochleae, according to dosimetric comparisons.

Whenever pediatric radiation oncologists define a target for WVI, the inclusion of the prepontine cistern is always a matter of concern. In general, the prepontine cistern is included within the radiation volume only when a third ventriculostomy is performed. Mailhot et al. [2] surveyed the structural inclusion and definition of whole ventricle volume and found that more than 50% of pediatric radiation oncologists did not include the prepontine cistern for WVI. Only 33% favored including the prepontine cistern, and only for a third ventriculostomy. According to the Children’s Oncology Group contouring atlas for WVI [3], the inclusion of the prepontine cistern is optional, but should be considered for patients who have undergone a third ventriculostomy and for those with large suprasellar tumors. In this light, the study by Ryu and Lee [1] represents a valuable addition to the understanding of whole ventricle volume.

With de-intensifying radiotherapy, such as the substitution of WVI for whole-brain irradiation, a significant volume of normal brain tissue can be spared and a decrease is expected in late treatment morbidities [4]. In addition, WVI, which applies to localized intracranial germinoma, has been reported with satisfactory results [5-7]. However, we know that there is room for further reduction of late complications by excluding the hippocampi or temporal lobes from WVI, and more research is needed in the future to identify an eligible subset of germinoma patients. These efforts will play an important role in preserving various aspects of memory and emotional learning in young patients.

Even very low doses of radiation that are considered safe can potentially cause secondary cancer, and the “as low as reasonably achievable” concept should be followed in the treatment of pediatric...
brain tumors. Therefore, in addition to de-intensifying the radiation dose and volume by virtue of randomized trials, more attention should be paid to developing a radiation treatment methodology based on rich clinical experience, such as the study by Ryu and Lee [1]. This will provide confidence to pediatric radiation oncologists in their efforts to decrease late complications while preserving cure rates.

**Conflict of Interest**

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

**References**


Radiation enteritis is a kind of intestinal radiation injury in patients with pelvic and retroperitoneal malignancies after radiotherapy, and its occurrence and development process are very complicated. At present, studies have confirmed that intestinal microecological imbalance is an important factor in the formation of this disease. Abdominal radiation causes changes in the composition of the flora and a decrease in its diversity, which is mainly manifested by a decrease in beneficial bacterial species such as *Lactobacilli* and *Bifidobacteria*. Intestinal dysbacteriosis aggravates radiation enteritis, weakens the function of the intestinal epithelial barrier, and promotes the expression of inflammatory factors, thereby aggravating the occurrence of enteritis. Given the role of the microbiome in radiation enteritis, we suggest that the gut microbiota may be a potential biomarker for the disease. Treatment methods such as probiotics, antibiotics, and fecal microbiota transplantation are ways to correct the microbiota and may be an effective way to prevent and treat radiation enteritis. Based on a review of the relevant literature, this paper reviews the mechanism and treatment of intestinal microbes in radiation enteritis.

**Keywords:** Gut microflora, Radiation enteritis, Beneficial bacteria

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**Introduction**

Radiotherapy is a common and important clinical treatment for abdominal, pelvic, and retroperitoneal malignant tumors. In the process of effectively eliminating tumor cells, the high sensitivity of the intestine to radiation causes local intestinal mucositis and gut microbiota disorder in the irradiation field, thereby forming radiation enteritis [1]. Extensive use of radiation results in radiation damage in up to 75% of radiotherapy recipients [2]. Approximately 90% of patients receiving pelvic radiotherapy had permanent changes in bowel habits after radiotherapy, and 50% experienced a significant reduction in quality of life [3]. At present, with a deeper understanding of the gut microbiota in the occurrence and development of diseases, the mechanism of the gut microbiota in radiation enteritis has become a research hotspot. This article reviews the related studies of intestinal microbes and radiation enteritis, hoping to provide new ideas for improving the toxicity of radiotherapy.
Definition and Role of Gut Microbiota

“Gut microbiota” generally refers to the various microbial communities (bacteria, fungi, archaea, viruses, and protozoan hosts) within the gastrointestinal tract that colonize the intestine. Among these species, the main microbial species in the human intestine include *Firmicutes* and *Bacteroides*, followed by *Actinomycetes* and *Verrucomicrobia* [4]. The composition of the microbiota is unique to everyone, but it is not fixed. The gut microbiota is affected by the environment, living habits, diet, drugs, and other factors and interacts with the body through the entero-brain axis, entero-liver axis, and entero-lung axis, and it is an important regulator of the body’s metabolism and immune system. The interaction among the gut microbiota, host and external environment maintains a balanced state [5]. At the same time, normal gut microbiota has specific functions in host nutrient metabolism, xenobiotic, and drug metabolism, maintaining the structural integrity of the intestinal mucosal barrier, immunomodulation, and resistance to pathogens [6]. However, the gut microbiota are mainly manifested as a symbiotic relationship with the host, and when the intestinal ecological environment changes, it may cause gut microbiota disorders, making these commensal bacteria pathogenic [7].

Definition of Radiation Enteritis and Pathophysiologic Changes

1. Definition of radiation enteritis

Radiation enteritis, which refers to radiation therapy-induced injury to the intestinal epithelium, with or without mild inflammation, is one of the common complications after radiation therapy in patients with pelvic malignancy [8]. Radiation enteritis can be divided into acute radiation enteritis and chronic radiation enteritis according to the time and course of symptoms. Acute radiation enteritis usually occurs during radiotherapy or within 3 months after the initiation of treatment, with the highest incidence being more than 75%, which occurs between weeks 4 and 5. It is usually associated with intestinal dysfunction, and the main clinical symptoms include diarrhea, mucous excretion, urgency of defecation, posterior or tenseness and, in rare cases, bleeding [9-12]. The onset of chronic radiation enteritis is relatively late, with the first symptoms generally appearing 9–14 months after radiation exposure, but it can also occur at any time up to 30 years after radiation exposure, with an incidence of approximately 2% to 20%. The symptoms of chronic radiation enteritis are similar to those of acute radiation enteritis, but the bleeding is often more severe [12].

2. Pathophysiological changes in radiation enteritis

Radiation enteritis is caused by the dynamic interaction of intestinal microbiome changes, epithelial cell injury and repair, endothelial cell injury and remodeling, fibroplasia, and enteric nervous system changes. The basic pathological changes include two aspects: intestinal mucosal injury caused by radiation and vascular connective tissue injury caused by radiation vascular endothelial cells [5]. At the initial stage of injury, the proliferation and maturation of intestinal epithelial cells with the ability of rapid division appear abnormal, which leads to reduced mitosis of crypt cells and then leads to thinning of the intestinal mucosa and shortening of the intestinal villi. In addition, there are pathological changes such as telangiectasia, edema, and inflammatory cell infiltration, which eventually lead to intestinal mucosal congestion, edema and exudation, and the clinical manifestations mainly include abdominal distension, abdominal pain, diarrhea, tenesmus, constipation, and bloody stools with mucous. In the later stage, the endothelial cells of the submucosal arterioles of the intestine are swollen, hyperplastic and fibrotic, resulting in the formation of obliterating vasculitis, thereby causing ischemia and hypoxia of the intestinal wall tissue, followed by erosion and ulceration of the intestinal mucosa, hyperplasia of submucosal fibrous tissue, hyaline degeneration of smooth muscle and other pathological changes, finally leading to intestinal wall fibrosis and thickening, intestinal luminal stenosis, etc. This results in intestinal necrosis, intestinal fistula, intestinal perforation, and intestinal obstruction [13,14].

How Radiation Enteritis Affects Gut Microbiota

1. Effects of radiation enteritis on gut microbiota

Derrien et al. [15] compared the gut microbiota of mice in the radio-injured group and the control group, and the results showed that the proportion of *Salmonella* and *Verrucomicrobia* in the intestines of the mice in the radio-injured group increased significantly, while the proportion of *Firmicutes* decreased significantly. Further findings showed that the clinical manifestations of patients were closely related to gut microbiota imbalance. At the same time, Cui et al. [16] determined the relationship between the microbiota of radiation enteritis and radiation sensitivity through 16S rRNA sequencing and found that 6.5 Gy of whole-body radiation gamma radiation changed the community composition of the gut microbiota of C57BL/6 mice. It was further confirmed that the change in gut microbiota affected the survival of mice after radiation, mainly due to the change in the microbiome, which removed the expression of host lncRNAs and made the mice sensitive to radiation. In addition, Johnson et al. [17] surgically exposed the ileum...
of mice and received a single dose of 19 Gy of high-dose radiation, and found that the number of aerobic bacteria and *Lactobacillus* were significantly reduced in the gut approximately 2 hours after radiotherapy. Zhao et al. [18] performed a single dose of 10 Gy local high dose precise irradiation on the abdomen of mice, and demonstrated that abdominal radiation disrupted the balance of gut microbiota in mice and significantly reduced the diversity of gut microbiota. In conclusion, the study suggests that abdominal radiation induces gut microbiota dysregulation and reduces the survival rate of irradiated mice in animal models.

Wang et al. [10] analyzed the gut microbiota of 18 patients (the total dose of pelvic radiotherapy was 50.4 Gy in 1.8 Gy/fraction) with cervical cancer complicated with radiation enteritis during radiotherapy and found that the α diversity of the gut microbiota in the patients with radiation enteritis decreased, but the β diversity increased, among which the proportions of *Megamonas*, *Neosphe- nolipa*, and *Prevotella* increased significantly. Further analysis of the differences in the gut microbiota of the patients before and after radiotherapy showed that the numbers of *Coprooccus* and *Desulfovibrio* were significantly reduced after radiotherapy. Manichanh et al. [19] found that patients with radioactive enteritis who had grade 3 or above diarrhea had a significantly higher difference in gut microbiota than those who did not have diarrhea. The gut microbiota remained unchanged in 60% of the patients without diarrhea throughout radiotherapy. However, only 29% of the patients with diarrhea did not have mutations in their gut microbiota. Among them, the number of Bacteroides increased significantly in the gut microbiota of the radioactive enteritis patients with diarrhea symptoms, while *Actinomyces*-related bacteria were not detected in the radioactive enteritis patients without di- arrhea [20]. Existing research results show that the gut microbiota of patients with radiation enteritis is significantly translocated, the number of *Actinobacteria* and *Proteobacteria* is significantly increased, and many conditional pathogenic bacteria, such as *Enterococcus* and *Enterobacterales*, are included.

In summary, the study mentioned above shows that the gut micro- microbiota of the patients with radiation enteritis changes significantly in terms of composition and diversity. In the gut microbiota of the patients with radiation enteritis, the abundance of bacteria belonging to *Actinomyces* and *Proteobacteria* increased, and most of these bacteria are conditional pathogenic bacteria. The number of beneficial bacteria (such as *Lactobacillus*) from *Firmicutes* and *Bacteroidetes* decreased significantly. The decrease in the number of beneficial bacteria will promote the proliferation of opportunistic pathogens and promote the release of endotoxins, thus aggravating the intestinal inflammatory response, inducing damage to the intestinal mucosal barrier, and aggravating the disease of patients [21,22].

2. Effects of gut microbiota on radiation enteritis

In recent years, many basic and clinical studies at home and abroad have been conducted on the relationship between gut microbiota and radioactive intestinal injury caused by pelvic radiotherapy, and considerable conclusions have been drawn [22–26].

Gerassy-Vainberg et al. [23] transplanted fecal bacteria from mice in the irradiation group and the control group into germ-free mice and found that the fecal bacteria that was given to the germ-free mice in the irradiation group significantly increased the degree of damage to the intestinal mucosa compared with the fecal bacteria in the control group, and the inflammation score was also significantly increased. When intestinal epithelial cells from both groups were examined separately, the fecal bacteria in the irradiated mice induced a significant increase in interleukin-1β (IL-1β) expression, while the tumor necrosis factor (TNF)-α expression did not change. The fecal flora of the mice in the irradiated group and the control group were cocultured with HT29 human colon cancer epithelial cells. The results showed that the fecal flora of the mice in the irradiated group could significantly increase the expression levels of TNF-α and IL-1β in epithelial cells. To further verify the effect of IL-1β, the researchers added an IL-1β inhibitor to the ir- radiated mice and found that the degree of damage to the intestinal mucosa in the irradiated mice was significantly reduced com- pared with that in the control group. This suggests that IL-1β in- duced by gut microbiota imbalance caused by radiation injury plays an important role in the occurrence and development of radiation enteritis. In recent years, some studies have shown that gut micro- microbiota translocation can affect host metabolism, but the specific mechanism is not clear [24]. At the same time, animal studies have shown that mice treated with fecal transplants have higher survival rates and fewer toxic reactions observed during a 10-day course of radiation compared with conventional mice. This suggests that changing the composition of the gut microbiota can alter the gut’s susceptibility to radiation [16].

Chitapanarux et al. [22] administered pelvic radiotherapy at a total dose of 56 Gy in 1.8 Gy in combination with standard treat- ment of locally advanced cervical cancer with cisplatin 40 mg/m² per week to patients with FIGO stage IIB–IIIB cervical squamous cell carcinoma, orally administered live *Lactobacillus acidophilus* and *Bifidobacterium bifidum* 7 days before and daily throughout radiotherapy in patients with cervical cancer and showed that it reduced the incidence of radiation-induced diarrhea, reduced the use of antidiarrheal drugs, and improved the status of the patients’ stools. Ding et al. [25] analyzed patients who had received radia- tion therapy for cervical and endometrial cancer and had radiation intestinal damage, and the symptoms of radiation enteritis, i.e., di- arrhea, rectal bleeding, abdominal pain, and fecal incontinence,
were improved in the patients who received fecal microbiota transplantation. Mitra et al. [26] also found in a study of 35 patients with cervical cancer receiving radiotherapy and chemotherapy that the diversity of intestinal microbes in patients was positively correlated with intestinal function during treatment.

Radiation Enteritis Therapy

Currently, the treatment of radiation enteritis mainly includes nutritional support, drug therapy, regulation of intestinal flora, mucosal protection, anti-oxidation, prevention, and treatment of complications. Surgical treatment is required when medical treatment is ineffective (Fig. 1). We summarized the clinical treatment of radiation enteritis [16, 27-33] (Table 1).

1. Nutritional support

In the treatment of radiation intestinal injury, the value of parenteral nutrition combined with enteral support therapy has been widely recognized. In the early stage of the disease, patients generally have more severe diarrhea or gastrointestinal bleeding, at which time the intestine needs to rest. Therefore, fasting and parenteral nutrition support should be given [27]. The long-term administration of parenteral nutrition to patients can cause intestinal mucosal atrophy. Therefore, when patients have diarrhea and if their gastrointestinal bleeding and other symptoms are under control, they should transition to enteral nutrition in a timely manner. Because the supply of energy to patients through enteral nutrition is in line with the physiological function of the intestine, it is conducive to the repair of damaged intestinal mucosa and epithelial cells, thereby maintaining the barrier effect of the intestinal mucosa and significantly reducing the occurrence of intestinal infections [34].

2. Probiotics, Prebiotics

At present, with further research on gut microbiota, the use of probiotics and prebiotics to treat radiation enteritis has become a research hotspot. Probiotics are a class of living microorganisms, including bacteria and yeast, that play an important role in reducing intestinal damage, reducing the severity of intestinal inflammation, reducing the cell apoptosis rate, increasing lactase, shortening intestinal villi, and so on [29, 35]. At the same time, prebiotics are beneficial to the host. Prebiotics are defined as nondigestible, selectively fermented short-chain carbohydrates that allow for specific changes in the composition or activity of the gut microbiota [36]. Probiotics and prebiotics have been widely used in the prevention and treatment of important gastrointestinal diseases such as irritable bowel syndrome (IBS) and inflammatory bowel disease.

![Fig. 1. Radiation leads to the reduction of intestinal flora diversity and the treatments are available for radiation enteritis. Created by Biorender.com.](https://doi.org/10.3857/roj.2023.00346)
Table 1. Radiation enteritis therapy

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<th>Study</th>
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<th>Recommendations or indications</th>
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<tr>
<td>Bozetti et al. [27]</td>
<td>Nutritional support</td>
<td>Early fasting and parenteral nutrition support</td>
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<tr>
<td>Linn et al. [28]</td>
<td>Drug treatment</td>
<td>Oral probiotics and prebiotics</td>
</tr>
<tr>
<td>Kim et al. [29]</td>
<td>Drug treatment</td>
<td>The enema plus oral antibiotics</td>
</tr>
<tr>
<td>Yoshimizu et al. [31]</td>
<td>Hyperbaric oxygen therapy</td>
<td>Under high pressure, by breathing pure oxygen or high concentrations of oxygen</td>
</tr>
<tr>
<td>Cui et al. [16]</td>
<td>Fecal microbiota transplantation</td>
<td>Feces from healthy donors were isolated and cultured in vitro and transplanted into the patient's intestine</td>
</tr>
<tr>
<td>Hale et al. [32]</td>
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<td>Endoscopic and argon coagulation for hemorrhagic radiation proctitis</td>
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<tr>
<td>Ruiz-Tovar et al. [33]</td>
<td>Operative treatment</td>
<td>With severe radiation intestinal injury require surgery</td>
</tr>
</tbody>
</table>

3. Antibiotic use

Damage to the intestinal mucosal barrier from abdominal or pelvic radiation therapy can lead to gut microbiota translocation, flora imbalance and bacterial over reproduction, thus causing intestinal infection and aggravating abdominal pain and distension in patients. Pui et al. [39] conducted a randomized controlled trial of colon lavage and oral antibiotics or 4% formalin in patients with chronic hemorrhagic radiation proctitis following radiation therapy. It was found that the enema plus oral antibiotics group not only had improvements in their blood in stool and stool frequency, but this treatment also alleviated diarrhea, stool control ability, and other symptoms. Antibiotic cocktail (ABX) and metronidazole pre-treatment were beneficial to the re-speciation of the intestinal microorganisms in irradiated mice. Studies have confirmed that pre-treatment with an antibiotic cocktail can effectively reduce intestinal inflammation, prevent intestinal fibrosis, and ultimately improve the survival rate of radiation-induced mice [18]. The above results indicate that antibiotic preconditioning can effectively relieve intestinal microbial disturbance and intestinal injury caused by abdominal radiation.

4. Nonsteroidal anti-inflammatory drugs

Clinically, the anti-inflammatory drugs commonly used to treat radiation enteritis include aminosalicylic acids and steroids. Nonsteroidal anti-inflammatory drugs can effectively inhibit the formation and release of inflammatory mediators to inhibit the intestinal mucosal inflammatory response and reduce intestinal damage, so they are commonly used in the treatment of ulcerative colitis. At present, some research claims that these medications can reduce the symptoms of radiation enteritis. Jahraus et al. [30] conducted a study on 39 prostate cancer patients (the pelvic external beam radiation dose was at least 45 Gy in four fields, and the total tumor dose was at least 64 Gy) receiving pelvic radiotherapy. During the period from 5 days before radiotherapy to 2 weeks after radiotherapy, when balsalazide was taken compared with placebo, intestinal adverse reactions such as diarrhea, dysuria, weight loss, fatigue and nausea were significantly reduced. Kilic et al. [40] conducted a randomized controlled trial showing that sulfasalazine reduced the incidence of radiation enteritis. At the same time, in clinical practice, intestinal adverse reactions were significantly reduced in patients receiving pelvic radiotherapy with sulfasalazine. However, mesalazine and oxalazine were not effective in preventing radiation enteritis. Compared with the control group, mesalazine did not significantly reduce the incidence of radiation enteritis after radiation therapy, and oxalazine even increased the incidence of diarrhea [41,42]. Some studies have shown that glucocorticoids have a certain alleviating effect on radiation enteritis, while some studies have not shown a therapeutic effect in their use. At present, there is still no large sample evidence to confirm their role in the treat-
ment of radiation enteritis. However, in our clinical work, intravenous and topical application of steroids are still used, and they can relieve the symptoms of patients to a certain extent, especially the symptoms of anal pain.

5. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is the treatment of diseases by breathing pure or high oxygen levels under high pressure (above normal pressure). HBOT can significantly improve the oxygen supply at the site of intestinal trauma, thereby increasing the oxygen content, oxygen partial pressure and oxygen reserve of radioactive enteritis tissue. HBOT promotes microvascular formation in the normal tissue around the lesion and is the only method that can be considered to increase the number of blood vessels in the irradiated tissue [43,44]. At present, HBOT is also recommended as an adjunct therapy in some of the guidelines for radiation injury treatment of malignant tumors in gynecology and head and neck surgery [45]. HBOT can not only improve the intestinal inflammatory response and promote the healing of the intestinal mucosa but also has a certain preventive effect on radioactive intestinal injury. Yoshimizu et al. [31] reported the efficacy of five patients with radioactive rectal ulcers who received HBOT, all of whom showed significant improvement in symptoms and complete healing of ulcers without adverse reactions. Moreover, for hemorrhagic chronic radiation enteritis, HBOT combined with argon ion coagulation is more effective. Another study retrospectively analyzed 88 patients with radiation injuries, including 22 patients with radiation enteritis, and the average time interval from radiation therapy to the first symptom was 68 months. The subjective parameters of 22 patients before and after HBOT were analyzed, and 15 patients showed improvement (decreased score on the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic scale). Five patients maintained the same score, and two patients worsened [46]. It is important to note that limitations in the number of hyperbaric oxygen chambers limit the accessibility of this treatment.

6. Fecal microbiota transplantation

After radiotherapy, changes in the type and number of intestinal microbes were associated with radiotherapy injury. Fecal microbiota transplantation (FMT) refers to the transplantation of feces from a healthy donor into the intestines of patients after isolation and culture in vitro to change the composition of their gut microbiota and further affect the digestive, metabolic and immune functions of patients [16]. However, its mechanism of action is still not fully understood. Currently, it is believed that the mechanism may be to restore the disturbed microflora, which can significantly relieve the clinical symptoms of patients and further promote the damage and repair of the intestinal mucosa [47]. FMT is also used in Clostridium/Clostridium difficile infections, inflammatory bowel disease, irritable bowel syndrome, and hepatic encephalopathy [48]. Studies have shown that FMT can relieve symptoms of radiation enteritis and improve gastrointestinal function. Cui et al. [16] transplanted gut microbiota from healthy mice into the intestines of radiation-damaged mice and found that it could increase the gastrointestinal function and epithelial cell integrity of radiation-damaged mice while maintaining the diversity of gut microbiota in irradiated mice. Ding et al. [25] found that three out of five patients with radioactive enteritis who received fecal microbiota transplantation showed significant relief in clinical symptoms and endoscopic manifestations. However, the relief of symptoms could not be maintained, and FMT might be required again. In addition, the study included a small number of cases and no control group. Whether microflora transplantation can be applied to clinical practice in the future still needs to be verified by further clinical studies with large samples.

7. Endoscopic and argon coagulation therapy

Endoscopy and argon coagulation are also commonly used for severe erosion of the intestinal mucosa, ulcers, and intractable hematochezia in radioactive enteritis. In addition, radiofrequency ablation, cryoablation and other treatments have also been reported.

8. Operative treatment

Serious complications such as intestinal obstruction, intestinal necrosis or intestinal perforation may occur when the condition of radioactive intestinal injury progresses to the advanced stage, which will seriously endanger the life and safety of patients. At this time, surgical treatment is the main treatment method. Ruiz-Tovar et al. [33] and Boland et al. [49] showed that approximately one-third of patients with chronic radiation intestinal injury required surgery. More than 50% of patients with severe radiation intestinal injury require surgery to relieve their symptoms.

Conclusion

The gut microbiota is closely related to radiation enteritis, but the current study is too shallow to elaborate its mechanism. More mechanistic studies are needed to provide evidence for alleviating radiation enteritis. While the studies provide interesting insights into the relationship between radiation enteritis and the gut microbiota, some of the limitations of the research should be acknowledged. Of the existing studies, most are based on animal models or small samples of human patients, and lack of control groups in some studies. And moreover, there could be differences
between mouse and human gut microbiota. At present, probiotics, antibiotics, and FMT have been used in the clinical treatment of radiation enteritis, but more basic research and clinical trials are needed to evaluate their efficacy and safety. Therefore, in the following study, we will conduct a prospective study on patients with radiation enteritis with different treatment methods and stages.

**Statement of Ethics**

As this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

**Conflict of Interest**

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

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**Author Contributions**


**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**References**

Proton therapy for reducing heart and cardiac substructure doses in Indian breast cancer patients

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Purpose: Indians have a higher incidence of cardiovascular diseases, often at a younger age, than other ethnic groups. This higher baseline risk requires consideration when assessing additional cardiac morbidity of breast cancer treatment. Superior cardiac sparing is a critical dosimetric advantage of proton therapy in breast cancer radiotherapy. We report here the heart and cardiac-substructure dos es and early toxicities in breast cancer patients treated post-operatively with proton therapy in India’s first proton therapy center.

Materials and Methods: We treated twenty breast cancer patients with intensity-modulated proton therapy (IMPT) from October 2019 to September 2022, eleven after breast conservation, nine following mastectomy, and appropriate systemic therapy, when indicated. The most prescribed dose was 40 GyE to the whole breast/chest wall and 48 GyE by simultaneous integrated boost to the tumor bed and 37.5 GyE to appropriate nodal volumes, delivered in 15 fractions.

Results: Adequate coverage was achieved for clinical target volume (breast/chest wall), i.e., CTV, and regional nodes, with 99% of the targets receiving 95% of the prescribed dose (V95% > 99%). The mean heart dose was 0.78 GyE and 0.87 GyE for all and left breast cancer patients, respectively. The mean left anterior descending artery (LAD) dose, LAD D0.02cc, and left ventricle dose were 2.76, 6.46, and 0.2 GyE, respectively. Mean ipsilateral lung dose, V5Gy, V20Gy, and contralateral breast dose (Dmean) were 6.87 GyE, 14.6%, 36.4%, and 0.38 GyE, respectively.

Conclusion: The dose to heart and cardiac substructures is lower with IMPT than published photon therapy data. Despite the limited access to proton therapy at present, given the higher cardiovascular risk and coronary artery disease prevalence in India, the cardiac sparing achieved using this technique merits consideration for wider adoption in breast cancer treatment.

Keywords: Breast cancer, Pencil beam scanning, Protons, Heart, Proton beam therapy, Toxicity

Introduction

Cardiovascular disease has an earlier onset and a more lethal course in Indians and other South Asians than in other population groups; this propensity has been noted to persist even in the diaspora [1]. In addition, a significant number of Indians suffer from diabetes and hypertension, both of which increase the propensity for cardiovascular ailments [2].

Even as the incidence of breast cancer rises [3], mortality due to the disease has declined [4]. A recently published audit of more than 2,000 breast cancer patients treated in a single year, at one of India’s largest cancer centres, documented a 5-year disease-free survival of 85% for early and 68% for locally advanced breast cancer patients, respectively [5]. This makes the issues of survivorship
relevant; one of these is treatment-related cardiac side-effects [4].

Cardiac ailments account for the highest number of non-cancer deaths in breast cancer patients. Deaths from cardiac causes constitute 10.1% of all deaths within one year and 19%, i.e., nearly a fifth of all deaths in patients surviving > 10 years after breast cancer diagnosis [6].

Several systemic treatments, such as adriamycin, taxanes, trastuzumab, and letrozole are cardiotoxic [7-10]. Though the cardiotoxicity of radiotherapy has declined due to the development of better techniques [11] it remains relevant, with dose-volume parameters being better understood now.

Darby et al. [12] defined acute coronary events (ACEs) as the diagnosis of myocardial infarction, coronary revascularization, or death resulting from ischemic heart disease after completion of treatment. The authors noted a 7.4% increase in the relative risk of an ACE for every 1 Gy increase in mean heart dose with no lower threshold of radiation dose for these events. Prior ischemic heart disease (IHD) markedly increased the odds of an ACE 6.67 times; hypertension, diabetes, chronic obstructive pulmonary disease (COPD), obesity and smoking also nearly doubled the risk, even with no history of IHD.

Subsequent to Darby’s landmark study [12], there has been a further analysis on the dose-volume relationship of cardiac toxicity and the dose received by cardiac substructures; coronary arteries and the left ventricle have emerged as organs-at-risk (OARs) [13,14]. In a prospective study by Abraham et al. [14], 17% of left-sided breast cancer patients, with only a small fraction receiving adriamycin and trastuzumab, had some form of cardiac ailment.

A review of mean heart doses published after 2014 has noted a mean heart dose of 3.6 Gy for left-sided breast cancer patients and 4.8 Gy in left-sided patients receiving a boost with proton therapy [15]. In contrast, mean heart doses in both dosimetric and clinical studies of proton therapy for breast cancer, are <1.5 Gy and <1 Gy for left and right-sided lesions, respectively [16]. Proton therapy, delivered by enface beams, is an elegant method to treat the breast/chest wall while reducing the dose to the heart and cardiac substructures [17,18]. Mutter et al. [19] have published a consensus statement that comprehensively discusses the role, technique & impact of proton therapy across various clinical scenarios.

Proton therapy has recently become available in India. A prospective registry HYPRO-B has been initiated to document the impact of proton therapy in Indian breast cancer patients. We report the dosimetric and early clinical outcomes of 20 consecutive breast cancer patients treated using pencil beam-based proton therapy in the region’s first proton therapy center.

Materials and Methods

Proton therapy was initiated in January 2019 and the first breast patient was treated in October 2019. We reviewed the details of 20 consecutive patients treated for breast cancer with proton therapy. The latter 16 patients were included in the HYPRO-B registry (Hypo-fractionated PROton therapy in Breast cancer). This study was approved by the Institutional Ethics Committee-Biomedical Research, Apollo Hospitals, Chennai, India (IEC No. API-I-C-S-004110-20). All patients were treated after informed consent.

1. Proton therapy planning and delivery protocol

Patients were immobilized in the supine position, with arms above the head on a breast board (Access Supine Breast Device, Avondale, PA, USA), and a planning CT was performed with axial images of 2 mm thickness on Canon Aquilion LB CT scanner.

The clinical target volume (CTV) structures, including whole breast/chest wall and nodal volumes, were contoured as per the RTOG atlas [20]; these were clipped 5mm (for the whole breast) and 3 mm (for chest wall) from the skin, respectively. In one patient the chest wall volume was not clipped, because of the involvement of dermal lymphatics. The supraclavicular lymph node region extended to the midline medially, the cricoid superiorly, trapezius posteriorly and followed the medial edge of the clavicle laterally. OARs, including the heart, left lung, right lung, esophagus, and thyroid, were contoured. Fifteen cardiac segments (five left ventricular and 10 coronary arterial segments) were delineated as per the cardiac contouring atlas described by Duane et al. [21]. A 3–5 mm rib ring was contoured outward from the rib pleural interface to encompass the rib cage.

Proton therapy treatment was planned on a RayStation treatment planning system (version 9.0; RaySearch Laboratories AB, Stockholm, Sweden). The dose prescription was 40 GyE to whole breast/chest wall, 48 GyE simultaneous integrated boost (SIB) to tumour bed and 37.5 GyE to nodal volumes, supraclavicular region, axilla & internal mammary chain (IMC) in 20 fractions. The first four patients were treated with a more protracted 20-fraction regime. Standard fractionation of 50 Gy in 2 Gy per fraction was advised to patients with a rheumatoid disorder or a silicone implant in situ. Two en-face beams were used with a hinge angle of 20°–30° (Fig. 1). A water-equivalent 4 cm Lucite range shifter was used for each beam. The CTV was robustly optimized for a 3-mm setup and 3.5% range uncertainty. Both dose computation and optimization used a Monte Carlo algorithm. An average relative biological equivalent (RBE) of 1.1 was used and all patients were planned with single-field optimization (SFO) technique. The planning goal considered was ideal target coverage of CTV, i.e., 97% of the target...
to receive at least $>95\%$ of the prescribed dose.

Treatment was delivered using pencil beam scanning protons on Proteus Plus machine (IBA, Louvain-La-Neuve, Belgium), where in each energy layer is scanned (from $-X$ to $+X$ direction of every $Y$ coordinate) as seen in the beam’s eye view (BEV) of particular beam geometry. For proton energies between 70.22 and 226.2 MeV, the in-air $X$ ($Y$) spot sigma at the isocenter ranges from 2.96 (3.00) to 6.68 (6.52) mm.

Treatment was delivered 5 times a week, with daily CBCT based image guided repositioning and intra-treatment monitoring using AlignRT (version 5.1.2; VisionRT, London, UK) based surface guidance. AlignRT is integrated with beam delivery system of Proteus Plus using universal beam triggering interface (UBTI). It allows pausing of the beam when the breathing amplitude of the patient exceeds the set threshold ($\pm 3$ mm).

2. Outcome assessment

1) Dosimetric
Coverage and OAR doses were documented as per dose prescription. Proton therapy plans were assessed for coverage of CTV 40 Gy, 37.5 Gy, 48 Gy by 95\% of prescription dose, mean heart dose, mean and D$_{0.02cc}$ of left anterior descending artery (LAD) and right coronary artery (RCA), D$_{max}$ oesophagus, D$_{max}$ spinal cord, mean lung dose, mean ipsilateral and contralateral lung dose, V$_{20Gy}$ and V$_{5Gy}$ ipsilateral and contralateral lung and mean contralateral breast dose.

2) Clinical
All patients were reviewed weekly once during radiation therapy, 4 weeks after therapy and then at 3 monthly intervals.

Results

Eleven patients received proton therapy following breast-conserving surgery (BCS), one after a skin-sparing mastectomy and the remaining received radiation following a mastectomy (Table 1). One patient did not require regional nodal irradiation. Among the 19 patients requiring nodal irradiation, nine received composite irradiation to three nodal regions; axillary radiation was omitted in the remaining 11 patients. All patients undergoing proton therapy after BCS received a boost to the tumour bed.

Adjuvant/neoadjuvant systemic treatment included adriamycin in 13, taxanes in 16, and trastuzumab in five. The remaining patients received hormone therapy alone.

Cardiovascular risk factors were present in six patients, diabetes in two, hypertension in three, rheumatoid arthritis in two, obesity in one and previous heart ailment in one patient, respectively; four patients had multiple risk factors ($>1$).

1. Target
Proton therapy achieved adequate dose coverage of breast/chest wall, i.e., CTV$_{40\%}$ with a mean 99\% of the target receiving 95\% of the prescribed dose ($V_{95\%} > 99\%$). Similarly, 99\% of the regional nodes (internal mammary, supraclavicular, and axilla) atleast 95\% of the prescribed dose. The OAR doses and $V_{95\%}$ of the target are shown in Fig. 2 and Tables 2, 3. The dosimetric outcomes of patients had internal mammary nodal irradiation are shown in Fig. 3.

2. OAR
The mean heart dose was 0.78 GyE, 0.41 GyE in patients with right-sided cancer and 0.88 GyE in patients with left-sided cancer. Among left-sided patients, the mean heart dose was 0.991 GyE for patients receiving chest wall proton therapy and 0.79 GyE for patients being irradiated following BCS; this was 0.475 GyE and 0.345 GyE, respectively, for right-sided patients. The mean ipsilateral lung dose was 6.84 GyE, $V_{15}$ of 14.6\%, and $V_{5}$ of 36.4\%.

3. Cardiac substructures
The mean LAD dose of the cohort was 2.76 GyE. The high-dose region likely to correlate with the location of coronary stenosis was analyzed as the minimum dose received by 0.02 cc (D$_{0.02cc}$) and was
Table 1. Patient characteristics (n = 20)

<table>
<thead>
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</tr>
<tr>
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<tr>
<td>Diabetes</td>
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</tr>
<tr>
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<td>Left</td>
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<tr>
<td>Right</td>
<td>4</td>
</tr>
<tr>
<td>Quadrant</td>
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</tr>
<tr>
<td>Upper outer</td>
<td>7</td>
</tr>
<tr>
<td>Lower outer</td>
<td>4</td>
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<td>Upper inner</td>
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<td>Retro areolar</td>
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</tr>
<tr>
<td>Surgery</td>
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</tr>
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<td>MRM</td>
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</tr>
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<td>Reconstruction using flaps</td>
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</tr>
<tr>
<td>Any nodal irradiation</td>
<td>19</td>
</tr>
<tr>
<td>3 nodal stations treated</td>
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</tr>
<tr>
<td>(internal mammary chain +</td>
<td></td>
</tr>
<tr>
<td>supraclavicular fossa + axilla)</td>
<td>9</td>
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<tr>
<td>Neo-adjuvant chemotherapy</td>
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<tr>
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</tr>
<tr>
<td>AC → paclitaxel + trastuzumab</td>
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<td>TCHP</td>
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<tr>
<td>Adjuvant chemotherapy</td>
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</tr>
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<td>AC → paclitaxel</td>
<td>5</td>
</tr>
<tr>
<td>AC → paclitaxel + trastuzumab</td>
<td>2</td>
</tr>
<tr>
<td>Hormonal therapy alone</td>
<td>4</td>
</tr>
</tbody>
</table>

BCS, breast-conserving surgery; MRM, modified radical mastectomy; AC, doxorubicin plus cyclophosphamide; TCHP, trastuzumab, pertuzumab, carboplatin, and docetaxel.

Doxorubicin 60 mg/m², cyclophosphamide 600 mg/m², paclitaxel 80 mg/m², carboplatin area under curve 5 or 6, trastuzumab starting dose 4 mg/kg followed by 6 mg/kg maintenance dose, pertuzumab starting dose 840 mg/kg followed by 420 mg/kg maintenance dose.

5. Toxicities and outcomes

One patient had grade 2 dysphagia. Two patients had grade 2 and one, grade 3 dermatitis. The latter occurred in the patient in whom the chest wall contour was not clipped on account of the involvement of dermal lymphatics. The skin reactions required dressing with a hydrocolloid patch and resolved 10 days after completion of therapy. On median follow-up of 12.5 months, the locoregional control an overall survival was 100%.

Discussion and Conclusion

Our data on dosimetric and early clinical outcomes documents the first Indian experience of proton therapy for breast cancer. Our results document consistently low heart and cardiac substructure doses. These are particularly relevant in the background of a high prevalence of cardiovascular risk factors among Indians and other South Asians. These are a significant prevalence of obesity, 44%–72% [22,23] in certain communities, diabetes in > 20% of the urban population [24] and a high age-standardized prevalence of hypertension and cardiovascular disease [25]. In our cohort of patients, six patients had cardiovascular risk factors, of which four patients had > 1 risk factor.

In addition, patients in India are less likely to be screen-detected, a significant proportion thus requiring anthracyclines and trastuzumab [3]. The additive effect of these cardiotoxic drugs, on the risk of cardiac disease, has been documented in several studies [26].

Proton therapy offers dosimetric advantages in cardiac, opposite breast and lung doses over conventional radiotherapy in the treatment of breast cancer, this being first postulated in 1999. The advantage of protons lies in the abruptness of the energy deposition (i.e., Bragg peak) and therefore sparing of distal tissues, like the heart and lungs. Several dosimetric studies have underlined the advantage of proton therapy in reducing the mean dose to the heart in comparison with 3DCRT, IMRT, helical tomotherapy, and VMAT [27–32] (Table 4). Notably, with target coverage remaining adequate and equivalent to photons, the range of reduction in the mean dose to the heart is approximately 73%–90%. The reduction of heart dose by protons is expected to significantly reduce the relative risk of ACEs [12].

This is especially relevant for patients with the cardiovascular risk factors noted above. The correlation of cardiovascular risk factors with a doubling of the risk of ACE has already been elucidated in the landmark study by Darby et al. [12], Jacobse et al. [33], who studied exclusively, the risk of myocardial infarction, also identified that hypertension and BMI ≥ 30 kg/m² were the only individual patient-related cardiovascular risk factors significantly associated with an increased myocardial infarction (MI) rate.

4. Equivalent dose in 2 Gy (EQD2)

The EQD2 of the mean heart dose ranged from 0.15 to 0.62 GyE. The range for the mean LAD dose was 0.12–8.2 GyE (EQD2), and the max LAD dose was 0.01–23.7 GyE (EQD2).

The mean left ventricular dose $V_{500}$ is documented in Table 3. This was low in post-BCS proton therapy (i.e., 0.37%) and as well as in post mastectomy proton therapy (i.e., 1.02%).

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Fig. 2. Radiation dose color wash of (A) right breast post-BCS, (B) left breast post-BCS, (C) right chest wall (with reconstruction), and (D) left chest wall, at the level of the left ventricle, showing coronary arterial segments and left ventricular myocardial segments. BCS, breast conservation surgery; RCA, right coronary artery; LAD, left anterior descending artery; RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.

Fig. 3. Dosimetry of patients with internal mammary nodal irradiation. IMN, internal mammary nodal; LAD, left anterior descending artery; RCA, right coronary artery.

IMN radiation (n=19)

Right sided (n=4)

Left sided (n=15)

Heart $D_{max}$: 0.80 GyE
LAD $D_{max}$: 2.27 GyE
$D_{0.02cc}$: 6.43 GyE
RCA $D_{max}$: 0.38 GyE
$D_{0.02cc}$: 2.43 GyE

Heart $D_{max}$: 0.41 GyE

Heart $D_{max}$: 0.90 GyE

RCA

LAD

RCA

LAD

$D_{mean}$: 0.72 GyE
$D_{0.02cc}$: 4.90 GyE

$D_{mean}$: 0.03 GyE
$D_{0.02cc}$: 0.20 GyE

$D_{mean}$: 0.29 GyE
$D_{0.02cc}$: 1.78 GyE

$D_{mean}$: 2.87 GyE
$D_{0.02cc}$: 8.09 GyE
1. Mean heart dose
The mean heart dose for left-side breast cancer in our study listed in Table 3 ranges from 0.11 to 1.2 GyE. Notwithstanding internal mammary nodal irradiation in 19 of 20 patients, the mean heart dose in our patients was 0.87 GyE for left-sided and 0.41 GyE for right-sided treatments, respectively (Table 2). Other relevant heart parameters $V_{5GyE}$, $V_{50GyE}$, mean dose to left ventricle (LV), LV $V_{5GyE}$, and mean dose to the LAD are 0.98%, 3.54%, 0.2 GyE, 0.74%, and 2.76 GyE, respectively.

2. Cardiac substructure dose
Thus far, there was a lack of clarity about the relative importance of sparing cardiac substructures, coronary arteries, versus myocardium versus both. This is reflected in the multiplicity of proposed dose constraints and cardiac structures [13,34,35]. Recently, however, relevant dose thresholds have been identified for the LAD and LV. Zureick et al. [36], treating a contemporary cohort of breast cancer patients, found that mean and max doses of LAD were correlated to adverse cardiac events in breast cancer patients. The potential dose threshold identified (by ROC curve analyses) for LAD $D_{max}$ was an EQD$_2$ of 2.8 Gy, and for LAD $D_{max}$ an EQD$_2$ of 6.7 Gy for any cardiac event. Similarly, the threshold dose for heart $D_{mean}$ was an EQD$_2$ of 0.8 Gy for any cardiac event [36]. It is important to note that only 12.5% of patients in this study received adriamycin, and < 10% received trastuzumab.

One of the distinct advantages of proton therapy is a reduction in dose to the LAD by as much as 90% compared to photon therapy (Table 4). The mean LAD dose achieved in our left-sided patients was 2.21 GyE, comparable with 2.8–5 Gy reported in various studies [14,36]. In our cohort, the mean and max LAD EQD$_2$ were less than the dose threshold identified by Zureick et al. [36] in 13 of 15 left-sided patients. In one patient, the $D_{max}$ for LAD was 36.25 GyE, because of the proximity of the LAD to the chest wall. We used the deep inspiratory breath hold technique for this patient and were able to reduce the $D_{max}$ of the LAD to 8.01 GyE.

The LV $V_5$ has been postulated to be a better correlate of cardiac dysfunction than the mean heart dose based on a retrospective study of 910 patients followed up for a median of 7.6 years by van den Bogaard et al. [13]. This parameter has only recently been addressed in published literature and was documented to range from 0 to 3.37% in this series. Abraham et al. [14], prospectively analyzed 181 breast patients, with a median follow-up of 127 months and recorded any cardiac events, viz., any ischemic event, conduction abnormality, congestive heart failure, pericarditis and valvular disease. The authors noted that mean left ventricular dose < 5.85 Gy (p = 0.035), $V_5 < 42$ cc (p = 0.024) and $V_{10} < 38$ cc (p = 0.081) reduces additional risk of radiation-related cardiac events to < 5% at 10 years. Using proton therapy, our mean left ventricular dose was 0.2 GyE. The absolute $V_5$ volume ranged from 0 to 3.7 cc.

3. Published data and ongoing studies
Clinical data published so far is detailed in Table 5 [17,18,37-44]. The largest cohort has been reported by the group at Massachusetts General Hospital, Boston, USA, with a documented locoregional failure rate of 1.6% at a median follow-up of 55 months in 69 evaluable patients treated with proton therapy [37]. The RAD-COMP trial [45] comparing protons with photons in breast cancer patients is accruing patients to determine the margin of benefit, with the end point of reduction in major cardiovascular events. The Mayo Clinic trial (NCT02783690) compares hypofractionated radiotherapy with standard fractionation in patients undergoing post-mastectomy proton therapy [46]. The Danish Breast proton therapy (NCT04291378) is recruiting patients to compare photon and proton radiotherapy for early breast cancer, the primary endpoint being cardiac events at 10 years [47]. We have instituted HY-PRO-B, CTRI/2020/11/029415, a prospective registry of patients undergoing hypofractionated proton therapy for breast cancer with the primary objective of determining ACEs at 5 years following hypofractionated proton therapy radiotherapy to the whole breast/chest wall. In addition, we plan to document locoregional control, quality of life, disease-free and overall survival, cardiac function

### Table 2. OAR dosimetry parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>$V_{5GyE}$</td>
<td>99.82 ± 0.26</td>
</tr>
<tr>
<td>$CV_{15}$</td>
<td>99.57 ± 0.70</td>
</tr>
<tr>
<td>$CV_{44}$</td>
<td>99.75 ± 28.30</td>
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<tr>
<td>Heart dose (GyE)</td>
<td>0.78 ± 0.33</td>
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<tr>
<td>Left sided patients</td>
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<tr>
<td>Right sided patients</td>
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</tr>
<tr>
<td>$V_{5GyE}$ (%)</td>
<td>0.98 ± 0.64</td>
</tr>
<tr>
<td>$V_{50GyE}$ (%)</td>
<td>3.54 ± 1.70</td>
</tr>
<tr>
<td>LAD (GyE)</td>
<td>2.76 ± 4.49</td>
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<tr>
<td>$D_{max}$ (GyE)</td>
<td>6.46 ± 7.40</td>
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<tr>
<td>LV (GyE)</td>
<td>0.20 ± 0.17</td>
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<tr>
<td>$V_{5GyE}$ (%)</td>
<td>0.74 ± 0.95</td>
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<tr>
<td>Ipsilateral lung (GyE)</td>
<td>6.87 ± 2.76</td>
</tr>
<tr>
<td>Contralateral breast dose (GyE)</td>
<td>0.38 ± 0.38</td>
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<tr>
<td>RCA (GyE)</td>
<td>0.38 ± 0.88</td>
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<tr>
<td>$D_{max}$ (GyE)</td>
<td>2.43 ± 4.45</td>
</tr>
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</table>

Values are presented as mean ± standard deviation. OAR, organs-at-risk; CTV, clinical target volume; LAD, left anterior descending artery; LV, left ventricle; RCA, right coronary artery.
Table 3. Target coverage and OAR dosimetry of 20 patients

<table>
<thead>
<tr>
<th>Laterality</th>
<th>Surgery</th>
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<th>Age (yr)</th>
<th>Target</th>
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<th>LAD</th>
<th>LV</th>
<th>RCA</th>
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<tr>
<td></td>
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<td></td>
<td>CTV$_{40\text{GyE}}$</td>
<td>CTV$_{30,50\text{GyE}}$</td>
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<td>Mean (GyE)</td>
<td>V$_{95%}$ (GyE)</td>
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<td>WB+SCF+IMC &amp; tumor bed boost</td>
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<td>100</td>
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<td>29</td>
<td>WB+tumor bed boost</td>
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<td>99</td>
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<td>WB+SCF+IMC &amp; tumor bed boost</td>
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<td>100</td>
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<td>4</td>
<td>52</td>
<td>WB+SCF+IMC+axilla &amp; tumor bed boost</td>
<td>99.9</td>
<td>99.8</td>
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<td>5</td>
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<td>WB+SCF+IMC+axilla &amp; tumor bed boost</td>
<td>99.8</td>
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<td>WB+SCF+IMC</td>
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<td>38</td>
<td>WB+SCF+IMC</td>
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<td>1.68</td>
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<tr>
<td></td>
<td></td>
<td>8</td>
<td>46</td>
<td>WB+SCF+IMC &amp; tumor bed boost</td>
<td>98.75</td>
<td>99.24</td>
<td>98.63</td>
<td>0.85</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>43</td>
<td>WB+SCF+IMC &amp; tumor bed boost</td>
<td>99.97</td>
<td>99.38</td>
<td>99.9</td>
<td>0.42</td>
<td>0.24</td>
</tr>
<tr>
<td>MRM</td>
<td></td>
<td>10</td>
<td>40</td>
<td>Chest wall+SCF+IMC+axilla</td>
<td>99.9</td>
<td>99.1</td>
<td>-</td>
<td>1.1</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>58</td>
<td>Chest wall+SCF+IMC</td>
<td>99.7</td>
<td>99.1</td>
<td>-</td>
<td>1.2</td>
<td>1.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>69</td>
<td>Chest wall+SCF+IMC</td>
<td>99.9</td>
<td>99.3</td>
<td>-</td>
<td>0.91</td>
<td>1.25</td>
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<tr>
<td></td>
<td></td>
<td>13</td>
<td>50</td>
<td>Chest wall+SCF+IMC+axilla</td>
<td>99.9</td>
<td>99.8</td>
<td>-</td>
<td>1.1</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>29</td>
<td>Chest wall+SCF+IMC+axilla</td>
<td>99.9</td>
<td>99.8</td>
<td>-</td>
<td>0.55</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>35</td>
<td>Chest wall+SCF+IMC+axilla</td>
<td>99.91</td>
<td>98.95</td>
<td>-</td>
<td>0.96</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td>42</td>
<td>Chest wall+SCF+IMC</td>
<td>99.81</td>
<td>97.86</td>
<td>-</td>
<td>1.12</td>
<td>0.82</td>
</tr>
<tr>
<td>Right sided</td>
<td>BCS</td>
<td>17</td>
<td>30</td>
<td>WB+SCF+IMC &amp; tumor bed boost</td>
<td>99.9</td>
<td>99.6</td>
<td>99.9</td>
<td>0.58</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>52</td>
<td>WB+SCF+IMC &amp; tumor bed boost</td>
<td>99.7</td>
<td>97.5</td>
<td>99.4</td>
<td>0.11</td>
<td>0</td>
</tr>
<tr>
<td>MRM</td>
<td></td>
<td>19</td>
<td>68</td>
<td>Chest wall+SCF+IMC</td>
<td>99.8</td>
<td>98.5</td>
<td>-</td>
<td>0.44</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>58</td>
<td>Chest wall+SCF+IMC+axilla</td>
<td>99.9</td>
<td>99.8</td>
<td>-</td>
<td>0.51</td>
<td>0.4</td>
</tr>
</tbody>
</table>

OAR, organs-at-risk; BCS, breast-conserving surgery; MRM, modified radical mastectomy; CTV, clinical target volume; LAD, left anterior descending artery; LV, left ventricle; RCA, right coronary artery; WB, whole breast; SCF, supraclavicular field; IMC, internal mammary chain; V$_x$, the volume of organ receiving $\geq x$ Gy; D$_{10\text{cc}}$, minimum dose received by x% (or cc) of the organ.
Table 4. Dosimetric studies showing OAR doses comparing proton therapy with other radiation techniques

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Surgery</th>
<th>n</th>
<th>Dose prescription</th>
<th>Technique</th>
<th>Heart dose parameter</th>
<th>LAD (Gy)</th>
<th>Ipsilaterial lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ares et al. [27], 2010</td>
<td>Breast conservation, mastectomy</td>
<td>20</td>
<td>50 Gy/25 fx</td>
<td>IMPT</td>
<td>Mean: 1.5 Gy</td>
<td>Mean: 7.5 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$V_{5\text{Gy}}$: 3.5%</td>
<td>$V_{20\text{Gy}}$: 7.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 10.5 Gy</td>
<td>Mean: 13.5 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$V_{5\text{Gy}}$: 36.5%</td>
<td>$V_{20\text{Gy}}$: 11%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 9.5 Gy</td>
<td>Mean: 20 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$V_{5\text{Gy}}$: 9.5%</td>
<td>$V_{20\text{Gy}}$: 40%</td>
<td></td>
</tr>
<tr>
<td>Fagundes et al. [28], 2015</td>
<td>Mastectomy</td>
<td>10</td>
<td>50.4 Gy/28 fx</td>
<td>Uniform scanning</td>
<td>Mean: 1.2 Gy</td>
<td>Mean: 7 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Max: 27.6 Gy</td>
<td>Mean: 20 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$D_{1.2cc}$: 14.9 Gy</td>
<td>$V_{20\text{Gy}}$: 28.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 8.2 Gy</td>
<td>Mean: 41.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Max: 15.5 Gy</td>
<td>Mean: 27.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$D_{1.2cc}$: 27.8</td>
<td>$V_{20\text{Gy}}$: 58%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 10.2 Gy</td>
<td>Mean: 58.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Max: 14.8 Gy</td>
<td>Mean: 25.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$D_{1.2cc}$: 26.6</td>
<td>$V_{20\text{Gy}}$: 58.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 6.8 Gy</td>
<td>Mean: 40.4%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Max: 41 Gy</td>
<td>Mean: 66.4%</td>
<td></td>
</tr>
<tr>
<td>Stick et al. [29], 2017</td>
<td>Breast conservation</td>
<td>41</td>
<td>50 Gy/25 fx</td>
<td>PBS-SFO</td>
<td>Mean: 0.3 Gy</td>
<td>Mean: 3.5 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3DCRT</td>
<td>Mean: 1.9 unit</td>
<td>Mean: 3.5 Gy</td>
<td></td>
</tr>
<tr>
<td>Speleers et al. [30], 2019</td>
<td>Breast conservation</td>
<td>10</td>
<td>40.5 Gy/16 fx</td>
<td>PBS-supine</td>
<td>Mean: 1.02 Gy</td>
<td>Mean: 3.4 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 5.6 Gy</td>
<td>Mean: 21.4 Gy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 1.08 Gy</td>
<td>Mean: 2 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 4.3 unit</td>
<td>Mean: 2.4 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 6.2 Gy</td>
<td>Mean: 5.3 Gy</td>
<td></td>
</tr>
<tr>
<td>De Rose et al. [31], 2020</td>
<td>Breast conservation, mastectomy</td>
<td>20</td>
<td>50 Gy/25 fx</td>
<td>IMPT</td>
<td>Mean: 0.4 Gy</td>
<td>Mean: 6.2 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 3.9 Gy</td>
<td>Mean: 12.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 2.85%</td>
<td>Mean: 18%</td>
<td></td>
</tr>
<tr>
<td>Kowalski et al. [32], 2020</td>
<td>Breast conservation</td>
<td></td>
<td></td>
<td>IMPT</td>
<td>Mean: 2.59 Gy</td>
<td>Mean: 10.8 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 9.5 Gy</td>
<td>Mean: 12.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean: 16.6%</td>
<td>Mean: 16.6%</td>
<td></td>
</tr>
</tbody>
</table>

OAR, organs-at-risk; LAD, left anterior descending artery; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; VMAT, volumetric modulated arc therapy; PBS, pencil beam scanning; SFO, single field optimization; $V_x$, the volume of organ receiving $x$ Gy; NM, not measured.

and dosimetric analysis for the latter.

4. Cost–effectivity
We believe that the application of more sophisticated radiation treatment techniques based on better dosimetric parameters, in the absence of or preceding Phase III trials, has many precedents [48-50]. There are concerns about the cost of treatment without evidence of demonstrable benefit in overall survival thus far [51].

Models estimating the cost–effectivety of protons suggesting an advantage in patients with at least one coronary risk factor or a mean heart dose of 5 Gy or more are specific to country-based health systems [52]. In addition, cost–effectivity analyses may not be relevant for the individual patient and do not address benefits accruing from avoiding cardiac interventions besides percutaneous coronary intervention (PCI). Proton therapy may also become less expensive in the foreseeable future with the advent of single-room

https://doi.org/10.3857/roj.2023.00073
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Surgery</th>
<th>n</th>
<th>Dose prescription</th>
<th>Technique</th>
<th>Heart dose parameter</th>
<th>LV dose parameters</th>
<th>LAD/RCA</th>
<th>Contralateral breast</th>
<th>Ipsilateral lung</th>
<th>Grade 3 skin reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald et al. [38], 2013</td>
<td>Mastectomy +/- reconstruction</td>
<td>12</td>
<td>50.4 Gy/28 fx</td>
<td>Passive scattering</td>
<td>Mean: 0.44 Gy, ( V_{20}^{0.01%} ); 0.09 Gy, ( V_{20}^{0.00004%} )</td>
<td>Mean: 6 Gy, ( V_{20}^{12.7%} )</td>
<td>Mean: 0.29 Gy, ( V_{20}^{6.5%} )</td>
<td>Nil</td>
<td>Moist desquamation: 28.6%</td>
<td></td>
</tr>
<tr>
<td>Cuaron et al. [18], 2015</td>
<td>Breast conservation 4, 30 mastectomy +/- reconstruction 24, and WLE chest wall 2</td>
<td>30</td>
<td>50.4 Gy/28 fx</td>
<td>Uniform scanning</td>
<td>Mean: 0.88 Gy</td>
<td>For left-sided tumors (mean: 1 Gy, ( V_{20}^{1.16%} ))</td>
<td>Mean: 0.29 Gy, ( V_{20}^{6.5%} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeCesaris et al. [39], 2019</td>
<td>Breast conservation, mastectomy</td>
<td>39</td>
<td>45–50.4 Gy/25–28 fx</td>
<td>Pencil beam scanning</td>
<td>Mean: 0.6 Gy (left 0.7 Gy, right 0.4 Gy), ( V_{20}^{0.1%} )</td>
<td>LAD mean: 2.8 Gy, ( V_{20}^{13.9%} ), ( V_{5}^{4%} )</td>
<td>Mean: 5 Gy, ( V_{20}^{13%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al. [40], 2019</td>
<td>Mastectomy + reconstruction</td>
<td>51</td>
<td>50 Gy/25 fx</td>
<td>Pencil beam scanning</td>
<td>Mean: 0.9 Gy, ( V_{20Gy}^{0.8%} )</td>
<td>Mean: 5 Gy, ( V_{20Gy}^{17 Gy} )</td>
<td>Mean: 0.2 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutter et al. [41], 2017</td>
<td>Breast conservation, mastectomy</td>
<td>12</td>
<td>50 Gy/25 fx</td>
<td>Pencil beam scanning</td>
<td>Mean: 0.9 Gy</td>
<td>Mean: 5 Gy, ( V_{20Gy}^{17 Gy} )</td>
<td>Mean: 0.2 Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verma et al. [42], 2017</td>
<td>Breast conservation, mastectomy</td>
<td>91</td>
<td>50.4 Gy/28 fx</td>
<td>Uniform scanning and pencil beam scanning</td>
<td>Mean: 0.5 Gy (left 0.8 Gy, right 0.07 Gy)</td>
<td>Mean: 0.3 Gy, ( V_{20Gy}^{16.1%} ), ( V_{5}^{34%} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{14.5%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liang et al. [43], 2018</td>
<td>Breast conservation, mastectomy</td>
<td>23</td>
<td>50–50.4 Gy/25–28 fx</td>
<td>Passive scattering</td>
<td>Mean: 0.7 Gy (left 0.8 Gy, right 0.4 Gy), ( V_{20}^{0.1%} )</td>
<td>Mean: 0.3 Gy, ( V_{20Gy}^{16.1%} ), ( V_{5}^{34%} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{14.5%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo et al. [17], 2019 Mastectomy</td>
<td>42</td>
<td>50.4 Gy/28 fx</td>
<td>Uniform scanning</td>
<td>Mean: 0.5 Gy</td>
<td>Mean: 0.3 Gy, ( V_{20Gy}^{16.1%} ), ( V_{5}^{34%} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{14.5%} )</td>
<td>Nil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jimenez et al. [37], 2019</td>
<td>Breast conservation, mastectomy</td>
<td>69</td>
<td>45–50.4 Gy/25–28 fx</td>
<td>Passive scattering, pencil beam scanning</td>
<td>Mean: 0.5 Gy</td>
<td>Mean: 0.3 Gy, ( V_{20Gy}^{16.1%} ), ( V_{5}^{34%} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{14.5%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeCesaris et al. [44], 2021</td>
<td>Breast conservation, mastectomy</td>
<td>172</td>
<td>50.4 Gy/28 fx</td>
<td>Pencil beam scanning</td>
<td>Mean: 0.9 Gy (left 1.1 Gy, right 0.7 Gy, bilateral 1.3 Gy)</td>
<td>Mean: 0.3 Gy, ( V_{20Gy}^{16.1%} ), ( V_{5}^{34%} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{14.5%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present study Breast conservation, mastectomy</td>
<td>20</td>
<td>48, 40, and 37.5 Gy in 15 fx</td>
<td>Pencil beam scanning</td>
<td>Mean: 0.78 Gy</td>
<td>Mean: 0.2 Gy, ( V_{20Gy}^{4 Gy} )</td>
<td>Mean: 0.38 Gy, ( V_{20Gy}^{6.84 Gy} )</td>
<td>Mean: 1.16 Gy, ( V_{5}^{34%} )</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OAR, organs-at-risk; LV, left ventricle; LAD, left anterior descending artery; RCA, right coronary artery; WLE, wide local excision; \( V_x \), the volume of organ receiving \( \geq x \) Gy.
facilities [53].

The current case series and published data indicate that proton therapy fulfils the sound principles of better sparing of organs at risk with equivalent target coverage in breast cancer.

In conclusion, cardiac, lung and contralateral breast doses consistently documented to increase the morbidity of breast radiotherapy are significantly reduced by proton therapy. Early results of pencil beam scanning-based hypofractionated proton therapy with SIB merit the consideration of this treatment in managing breast cancer.

Acknowledgements

We thank Minnal Mookaiah (Radiotherapy Technologist) and Anusha T (Physician Assistant) for their contribution to this study. We also thank our patients and their families.

Statement of Ethics

This study was approved by the Institutional Ethics Committee-Biomedical Research, Apollo Hospitals, Chennai, India (IEC Application No. API–I–C–S–004110–20; Protocol No. APCC20203, Breast Cancer Proton Registry HyPro-B). Written informed consent was obtained from participants to participate in the study.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, Nangia S. Investigation and methodology, Nangia S, Burela N. Project administration, Nangia S. Resources, Sharma D, Noufal MP, Pato K, Wakde MG, Burela N, Nangia S. Supervision, Nangia S, Sharma D. Writing of the original draft, Nangia S, Burela N, Sharma D. Writing of the review and editing, Nangia S, Burela N. Software, Noufal MP, Burela N. Validation, Nangia S. Formal analysis, Burela N. Data curation, Burela N. Visualization, Nangia S.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Proton therapy in Indian breast cancer patients


Evaluation of the role of inflammatory blood markers in predicting the pathological response after neoadjuvant chemoradiation in patients with locally advanced rectal cancer

Shahram Manoochehry, Hamid Reza Rasouli, Fathollah Ahmadpour, Alireza Keramati

Trauma Research Center, Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

Purpose: This study aimed to evaluate the role of inflammatory blood markers in predicting the pathological response rate after neoadjuvant chemoradiation (neo-CRT) in patients with locally advanced rectal cancer (LARC).

Materials and Methods: In this prospective cohort study, we analyzed the data of patients with LARC who underwent neo-CRT and surgical removal of the rectal mass between 2020 and 2022 in a tertiary medical center. Patients were examined weekly during chemoradiation and neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune inflammation index (SII) were calculated from weekly laboratory data. Wilcoxon signed-ranks and logistic regression analysis were utilized to determine whether any laboratory parameters during different time point assessments or their relative changes could predict the tumor response based on a permanent pathology review.

Results: Thirty-four patients were recruited for the study. Eighteen patients (53%) achieved good pathologic response. Statistical analysis by Wilcoxon signed-ranks method indicated significant rises in NLR, PLR, MLR, and SII on weekly assessments during chemoradiation. Having an NLR over 3.21 during chemoradiation was correlated with the response on a Pearson chi-squared test (p = 0.04). Also, a significant correlation was found between the PLR ratio over 1.8 and the response (p = 0.02). NLR ratio over 1.82 marginally missed a significant correlation with the response (p = 0.13). On multivariate analysis, a PLR ratio over 1.8 showed a trend for response (odds ratio = 10.4; 95% confidence interval, 0.9–123; p = 0.06).

Conclusion: In this study, PLR ratio as an inflammatory marker showed a trend in the prediction of response in permanent pathology to neo-CRT.

Keywords: Rectal cancer, Inflammatory markers, Neoadjuvant chemoradiation

Introduction

Colorectal cancers are the third most common cancer in terms of incidence and the second leading cause of death due to cancer worldwide [1]. Out of every ten patients with colorectal cancer, almost four patients have rectal cancer [1]. Treatment of locally advanced rectal cancer (LARC) has evolved over the last 40 years. Currently, the standard treatment of colorectal cancer is neoadjuvant long-course chemoradiation (neo-CRT) followed by total mesorectal excision (TME) surgery after a waiting period of 8–12 weeks [2]. This treatment approach can reduce tumor size and local recurrence and improve patients’ overall survival (OS) and disease-free survival (DFS) [3]. Response to neo-CRT is an independent predictor of survival in rectal cancers [4]. After neo-CRT, patients will respond differently [5]. Approximately 15% of patients achieve a pathologic complete response (pCR) in which there will be no vi-
able tumor cells in the resected specimen [5]. Patients with pCR after neo-CRT have better OS and DFS than non-pCR patients [6,7]. We can use organ preservation approaches in pCR patients providing equivalent oncological outcomes with less morbidity and complications [8]. On the other hand, it is rational to resect non-responder patients sooner without having to wait for 8–12 weeks or consider alternative neoadjuvant treatments [9]. Therefore, it will be more beneficial to have the ability to predict the pathologic response rate of patients to neo-CRT with no time wasting.

In the studies conducted in recent years, researchers introduced multiple measurable blood biomarkers as potential predictors of response rate, but so far, no definitive relationship has been found [10-12]. Some of these studies reported meaningful relationship between the lymphocyte-to-monocyte ratio (LMR), carcinoembryonic antigen (CEA), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and pathologic response rate [11] while others did not found any association between these factors and response rate [10] and there are still contradictory results. In the most recent retrospective study, higher LMR was associated with a better response rate; meanwhile, higher NLR and PLR were observed in poor response rate patients [13].

This prospective study investigates the relationship between measurable tumor inflammation-related blood factors (NLR, LMR, total white blood cell count, and PLR) and pathological response rate to neoadjuvant therapy. The advantage of conducting this study compared to similar previous ones is the prospective design of this study and the use of standard and up-to-date chemoradiation in all eligible patients.

**Materials and Methods**

**1. Patients**

In this prospective cohort study, we analyzed patients with LARC who underwent standard neo-CRT and surgical removal of the rectal mass by TME between 2020 and 2022 in a tertiary medical center.

Patients were included in this study if they had all of these criteria: (1) rectal mass adenocarcinoma confirmed with colonoscopic biopsy; (2) confirmed clinical 7th edition of the American Joint Committee on Cancer staging of II/III by endoscopic ultrasonography or magnetic resonance imaging (MRI) with apparent diffusion coefficient/dynamic contrast enhanced protocol; (3) no evidence of metastatic disease in computerized tomography scan; (4) no previous history of pelvic radiotherapy, chemotherapy or target therapy of any kind; (5) no previous or current history of active connective tissue disorders; and (6) no active systemic inflammation. After assessing the patients for mentioned criteria, 34 patients were eligible to be recruited in this study.

This study was performed in line with the principles of the Declaration of Helsinki. The local Institutional Review Board of Baqiyatallah University of medical sciences and the hospital’s ethics committee approved the current study (No. IR.BMSU.BAQ.REC.1399.061, date 2021-03-02). Inform consent was obtained from all patients.

**2. Treatments**

All patients underwent long-course radiotherapy for 25 or 28 fractions of 1.8 Gy/fraction or 2.0 Gy/fraction and 5-fluorouracil (5FU)-based concurrent chemotherapy (capecitabine 825 mg/m² twice daily throughout the irradiation course). No additional cycle of chemotherapy was administered in the interval between the completion of radiotherapy and surgery.

Due to the cardiac side effects of the 5FU-based chemotherapy, cardiac counseling was requested for the patients. Radiotherapy was delivered with the four-field three-dimensional conformal radiation therapy (3DCRT) technique for all of the patients in this study. The treatment field consisted of the primary tumor and high-risk nodes of the pelvic region. Blood samples of patients were evaluated weekly from 1st week to 5th week during chemoradiation with respect to NLR, PLR, monocyte lymphocyte ratio (MLR), and immune inflammation index (SII). Surgery was performed after 8–12 weeks of radiotherapy, and all patients underwent standard TME. All patients received standard 4-month of adjuvant CepeOX (capecitabine and oxaliplatin) or FOLFOX (5FU, leucovorin, and oxaliplatin) chemotherapy based on the National Comprehensive Cancer Network guidelines.

**3. Data collection and definitions**

Pathologic response to neoadjuvant chemoradiotherapy was reported based on a 3-point tumor regression grade (TRG) system. Based on this scoring system, patients with no viable cancer cells in the primary tumor were defined as TRG0 or pCR. TRG1 was considered as single cells or microscopic residual cancer cells; TRG2 was defined as residual cancer with a desmoplastic response; TRG3 was defined as minimal evidence of tumor response. Patients with TRG0 or TRG1 were grouped as having a good response and patients with TRG2 or TRG3 were grouped as having a poor response. The location of the tumor was defined based on the distance between the anal verge and distal location of the tumor and then categorized into two main groups: lower rectum (less than 6 cm from the anal verge) and higher rectum (more than 6 cm from the anal verge). The inflammatory markers studied in this trial were calculated using mentioned formulas from acquired laboratory data:
NLR ratio: the ratio between 5th week NLR and 1st week NLR; PLR ratio: the ratio between 5th week PLR and 1st week PLR; MLR ratio: the ratio between 5th week PLR and 1st week MLR; SII ratio: the ratio between 5th week SII and 1st week SII.

4. Statistical analysis

Descriptive and frequency analyses were used. The continuous variables are expressed as median with 25th and 75th percentiles. We used Kolmogorov-Smirnov analysis to determine the normality of the quantitative data and it indicated that the data is non-normal. Wilcoxon signed-ranks method was used to assess the changes in pre-defined laboratory parameters and also comparing the laboratory values between two time points. Receiver operating characteristic curve analysis was used to determine the best cut-off points for the pre-defined quantitative laboratory parameters based on the maximum value achieved for the sum of sensitivity and specificity. Logistic regression analysis was also utilized to determine whether any lab parameters during different time point assessments or their relative changes could predict the tumor response based on a permanent pathology review. A p-value less than 0.05 was considered significant for all analyses. All the statistical analyses were conducted using IBM SPSS statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Thirty-four patients with a confirmed diagnosis of LARC were recruited for the study (Fig. 1), including 22 (62.9%) men and a mean ± standard deviation age of 58.9 ± 13.1 years. Table 1 depicts baseline patient and tumor characteristics (tumor stage, tumor location, diabetes, and smoking status).

All patients received 3DCRT to 50–54 Gy with 1.8–2 Gy dose per fraction in 5–5.5 weeks concurrently with capecitabine 825 mg/m² body square area twice daily during radiotherapy sessions. Patients underwent surgery within 8–12 weeks of the last radiotherapy session.

Eleven patients (32.4%) achieved pCR (TRG0). Seven patients (20.6%) achieved TRG1, whereas 16 patients showed poor response to neoadjuvant treatment according to the pathologic review (13 TRG2 and 3 TRG3).

The patients underwent blood tests weekly during chemoradiation. NLR, PLR, MLR, and SII were calculated for each patient during chemoradiation (Table 2).
Table 2. Analysis of weekly lab data during chemoradiation

<table>
<thead>
<tr>
<th></th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>2.5 (1.9–3.2)</td>
<td>4.7 (3.2–6.9)</td>
<td>3.1 (2.5–4.4)</td>
<td>4.7 (2.9–6.2)</td>
<td>4.7 (2.9–6.8)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>0.004*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>PLR</td>
<td>171.6 (133.7–227.1)</td>
<td>308.5 (192.7–394.8)</td>
<td>166.6 (141.0–240.1)</td>
<td>258.1 (165.2–308.4)</td>
<td>300.0 (228.0–468.0)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>0.126</td>
<td>0.004*</td>
<td>0.004*</td>
<td>0.004*</td>
</tr>
<tr>
<td>MLR</td>
<td>0.3 (0.2–0.5)</td>
<td>1.0 (0.3–1.3)</td>
<td>1.5 (1.0–2.4)</td>
<td>0.7 (0.4–1.1)</td>
<td>1.1 (0.6–1.6)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>0.001*</td>
<td>0.003*</td>
<td>0.003*</td>
<td>0.003*</td>
</tr>
<tr>
<td>SII</td>
<td>527976 (417694–838379)</td>
<td>1021250 (584726–1554667)</td>
<td>482800 (387195–834884)</td>
<td>864571 (587130–1079357)</td>
<td>890266 (604620–1288250)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>0.999</td>
<td>0.007*</td>
<td>0.007*</td>
<td>0.007*</td>
</tr>
<tr>
<td>Lymphocyte (10^3/mm³)</td>
<td>25.9 (21.2–30.7)</td>
<td>14.5 (10.3–20.0)</td>
<td>20.0 (16.0–25.0)</td>
<td>14.0 (11.0–23.0)</td>
<td>14.5 (10.7–20.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001*</td>
<td>0.003*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Neutrophil (10^3/mm³)</td>
<td>62.8 (58.0–69.5)</td>
<td>70.0 (65.3–74.0)</td>
<td>64.0 (66.5–70.0)</td>
<td>72.0 (65.0–77.0)</td>
<td>66.0 (62.3–70.0)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001*</td>
<td>0.727</td>
<td>0.010*</td>
<td>0.010*</td>
<td>0.036*</td>
</tr>
<tr>
<td>Platelet (10^3/mm³)</td>
<td>216.0 (179.0–252.0)</td>
<td>197.0 (170.0–244.0)</td>
<td>171.0 (149.0–199.0)</td>
<td>178.5 (154.7–210.7)</td>
<td>210.0 (168.0–244.0)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.070</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as median (25th–75th percentile). The values of Week 1 have been considered as reference value and the values for the following weeks have been compared with Week 1.
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic inflammatory index.

* p < 0.05.

Analysis by Wilcoxon signed-ranks method indicated significant rises in NLR, PLR, MLR, and SII on weekly assessments during chemoradiation.
As described before and according to the analysis, having an NLR over 3.21 on the last laboratory test during chemoradiation was correlated with the pathological response on a Pearson chi-squared test (χ² = 4.2, p = 0.04). Also, a significant correlation was found between the PLR ratio over 1.8 and pathological response (χ² = 5.25, p = 0.022). NLR ratio over 1.82 marginally missed a significant correlation with the pathological response (χ² = 2.33, p = 0.13).

Table 3 shows univariate/multivariate regression analysis of the inflammatory markers and pathologic response. As shown on multivariable analysis, a PLR ratio over 1.8 showed a trend for response prediction after controlling for confounders including age, sex, and clinical stage.

Discussion and Conclusion
Based on our findings, of the 34 LARC patients enrolled in this study, 53% had a good pathologic response (TRG0 and TRG1), and 47% had a poor response (TRG2 and TRG3) to neo-CRT treatment. Unlike most of the studies conducted so far, in this study, by performing weekly blood tests during treatment, it was possible to determine the blood cell ratios between different weeks of treatment. Based on the measurements performed in the present study, no correlation was found between the NLR, PLR, MLR, and SII measured based on laboratory tests before the treatment initiation or during the 1st week of radiotherapy and the rate of pathological response. On the other hand, in patients whose measured PLR ratio of the 5th week to the 1st week was more than 1.8, there was a higher clinical response rate to chemoradiation.

The current standard treatment for LARC patients consists of neoadjuvant radiotherapy and concurrent 5FU-based chemotherapy followed by delayed TME surgery [2]. Surgery can be delayed or eliminated in patients who have a good response to neoadjuvant treatment. On the other hand, in patients with poor response to neoadjuvant therapy, a more intensive approach such as total neoadjuvant therapy can be performed. Hence, the possibility of predicting the extent of pathological response to neoadjuvant treatment can significantly affect the treatment approach of patients. MRI and positron emission tomography (PET) scans are currently non-invasive methods for determining clinical response rates [14, 15]. Studies have shown that the conduction of PET scan after radiotherapy treatment significantly correlates with the clinical response rate [16, 17]. It is worth mentioning that the cost of performing these methods is much higher compared to performing blood sample tests. As response assessment by colonoscopy, MRI or PET is reserved for about 8 weeks after CRT, using inflammatory values and ratios initially and during CRT provides an earlier understanding of the potential capability of the patient to be a responder.

In LARC, the rate of response to treatment is not solely dependent on the initial stage of the disease or the demographic characteristics of the patients, and many factors are influential in deter-
in the current study, blood samples of patients were examined weekly during radiotherapy treatment, and inflammatory markers mining this response [18]. Additionally, the response occurs heterogeneously in different patients, even those with the same cancer stage [5,10]. So far, several studies have shown a significant relationship between inflammatory factors and the presence of cancers [19]. Also, a shred of evidence has been found in line with the existence of a relationship between these inflammatory factors and the ability to predict the prognosis or treatment response rate of the patients [20-26]. On the other hand, some contradictory and unpredictable correlations between response rate and inflammatory markers have been found in some current studies [27-30]. These controversial findings led us to investigate and assess the possible correlation between inflammatory blood markers in predicting the pathological response after neo-CRT in patients with LARC. Another issue to mention is that the exact mechanism supporting this relationship has not yet been entirely determined [31]. Currently, the biggest concern in using these non-invasive methods is the high probability of error in determining the patients with a complete pathological response.

NLR, PLR, MLR, and SII are the most common inflammatory blood factors studied. In a retrospective study by Wang et al. [13], evaluating 273 LARC, higher pretreatment NLR and PLR (measured based on lab data from 1 week before initiation of chemoradiation) were related to poor pathological response (p = 0.025 and p < 0.0001, respectively). These results were in line with another retrospective study by Li et al. [11], in which pretreatment NLR, PLR, and MLR were significant predictors of pCR. In contrast, in a retrospective study by Zhang et al. [32] conducted in China on 472 LARC, the high-NLR group had lower pCR rates, but the difference was not significant. Likewise, another study showed no significant correlation between pretreatment NLR and PLR with pathologic response rate [10].

In most studies carried out so far, the investigations have been done only on the laboratory tests before the initiation of the radiotherapy. This hypothesis is reasonable to calculate the tumor response rate to radiotherapy by comparing the laboratory tests done after the radiation with the tests before chemoradiation initiation at different time levels. As far as we know, the study by Lee et al. [33] in Korea was the only study that evaluated the patients’ laboratory tests at different time intervals during radiotherapy. In their retrospective study, patients’ laboratory tests were collected and analyzed at three stages; before chemoradiation, 3 weeks after the chemoradiation initiation, and 4 weeks after chemoradiation completion. Also, the changes in these values were investigated in different stages. Lee et al. [33] found a significant correlation between low pretherapy NLR, high intrathrapy NLR and PLR, high intratherapy NLR ratio (intratherapy NLR divided by pretherapy NLR), and PLR ratio (intratherapy PLR divided by pretherapy PLR) with pathological complete response.

In the current study, blood samples of patients were examined weekly during radiotherapy treatment, and inflammatory markers

### Table 3. Univariate/multivariate regression analysis of the inflammatory markers and pathologic response

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (0.98–1.08)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex</td>
<td>0.83 (0.20–3.41)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.24 (0.23–6.62)</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.83 (0.20–3.41)</td>
<td>0.80</td>
</tr>
<tr>
<td>Tumor location</td>
<td>0.87 (0.19–4.01)</td>
<td>0.85</td>
</tr>
<tr>
<td>Clinical T</td>
<td>0.58 (0.15–2.25)</td>
<td>0.43</td>
</tr>
<tr>
<td>Clinical N</td>
<td>0.65 (0.25–1.72)</td>
<td>0.38</td>
</tr>
<tr>
<td>NLR &gt; 3.21</td>
<td>6.00 (0.98–36.70)</td>
<td>0.05*</td>
</tr>
<tr>
<td>NLR ratio &gt; 1.82</td>
<td>3.30 (0.69–16.02)</td>
<td>0.13*</td>
</tr>
<tr>
<td>PLR &gt; 168</td>
<td>2.20 (0.30–15.30)</td>
<td>0.40</td>
</tr>
<tr>
<td>PLR ratio &gt; 1.80</td>
<td>6.60 (1.20–35.40)</td>
<td>0.03*</td>
</tr>
<tr>
<td>MLR &gt; 0.265</td>
<td>0.80 (0.10–5.80)</td>
<td>0.80</td>
</tr>
<tr>
<td>MLR ratio &gt; 1.46</td>
<td>1.80 (0.30–10.60)</td>
<td>0.50</td>
</tr>
<tr>
<td>SII &gt; 501065</td>
<td>2.20 (0.30–15.30)</td>
<td>0.40</td>
</tr>
<tr>
<td>SII ratio &gt; 1.39</td>
<td>1.50 (0.30–8.20)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic inflammatory index; PLR ratio, the ratio between 5th week PLR and 1st week PLR; NLR ratio, the ratio between 5th week NLR and 1st week NLR; CI, confidence interval; OR, odds ratio.

*p < 0.05.
such as NLR, PLR, MLR, and SII were calculated from these samples. Also, instead of analyzing a single pretreatment laboratory value for determining its correlation with the eventually achieved response, we investigated whether there was any correlation between the velocity of temporal changes in the mentioned values and the response. In a univariate analysis, our results showed that patients achieving a PLR on the 5th week of radiotherapy over 1.8 times the initial PLR (PLR ratio) are 6.6 times more likely to reach a complete or near-complete response on the permanent pathology. Moreover, this PLR ratio kept its significance on a multivariable analysis after considering the effect of confounders including age, sex, and initial clinical stage.

To our knowledge, this is the first prospective cohort that examined the weekly blood samples of patients during chemoradiation. In addition, due to the shorter sequence between samplings, it was possible to determine the details of changes in inflammatory factors during the course of radiotherapy for the first time. According to previous studies, chemotherapy in the interval between the completion of radiotherapy and surgery has increased the pathological response rate; therefore, patients who received chemotherapy outside the course of radiotherapy were not included in the study [34,35]. Likewise, the radiation treatment method and dose were common among patients. In addition, it is suggested that associated pathways and related genes be considered intelligent targets for treating rectal cancers at the molecular levels [36].

Several limitations need to be addressed in this study. First, the number of patients evaluated in this study was relatively small, and by increasing the number of patients examined, more robust results could probably be obtained. Second, to eliminate the interobserver error in determining the response rate, it would be better to review all pathology samples by a single pathologist.

In conclusion, our study showed that the magnitude of change in inflammatory markers, especially platelet to lymphocyte ratio, through the neo-CRT course can have a borderline effect on the prediction of complete/near-complete pathological response on the permanent pathology.

**Statement of Ethics**

This study was performed in line with the principles of the Declaration of Helsinki. The local Institutional Review Board of Baqiyatallah University of medical sciences and the hospital’s ethics committee approved the current study (No. IR.BMSU.BAQ.REC.1399.061, date 2021-03-02).

**Conflicts of Interest**

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

**Funding**

None.

**Author Contributions**


**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**References**


The effects of low-dose radiation therapy in patients with mild-to-moderate Alzheimer’s dementia: an interim analysis of a pilot study

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Purpose: We aimed to determine whether low-dose radiotherapy (LDRT) is effective in patients with Alzheimer disease (AD).

Materials and Methods: We included patients according to the following criteria: probable Alzheimer’s dementia according to the New Diagnostic Criteria for Alzheimer’s Disease; confirmation of amyloid plaque deposits on baseline amyloid positron emission tomography (PET); a Korean Mini-Mental State Examination 2nd edition (K-MMSE-2) score of 13–26; and a Global Clinical Dementia Rating (CDR) score of 0.5–2 points. LDRT was performed six times at 0.5 Gy each. Post-treatment cognitive function tests and PET-CT examinations were performed to evaluate efficacy. The medication for AD treatment was maintained throughout the study period.

Results: At 6 months after LDRT, neurological improvement was seen in 20% of patients. Patient #2 showed improvement in all domains of the Seoul Neuropsychological Screening Battery II (SNSB-II). Moreover, the K-MMSE-2 and Geriatric Depression Score-Short Form scores improved from 20 to 23 and from 8 to 2, respectively. For patient #3, the CDR score (sum of box score) improved from 1 (4.0) to 1 (3.5) at 3 months follow-up. Moreover, the Z scores for language and related functions, memory, and frontal executive function improved to -2.56, -1.86, and -1.32, respectively at the 6-month follow-up. Two patients complained of mild nausea and mild hair loss during LDRT, which improved after treatment.

Conclusion: One of the five patients with AD treated with LDRT experienced a temporary improvement in SNSB-II. LDRT is tolerable in patients with AD. We are currently under follow-up and will conduct cognitive function tests after 12 months after LDRT. A large-scale randomized controlled trial with a longer follow-up period is warranted to determine the effect of LDRT on patients with AD.

Keywords: Alzheimer’s disease, Dementia, Low dose radiotherapy

Introduction

Alzheimer’s disease (AD) is the most prevalent causative disease for dementia [1]. In 2017, there were approximately 50 million people with dementia worldwide, with this number being expected to double every 20 years [1]. AD is a neurodegenerative disease in-
volving complex interactions among amyloid-β, tau, and neuroinflammation. Although clinical trials have investigated the efficacy of drugs targeting amyloid-β and tau, there remains no effective treatment [2,3]. Acetylcholinesterase inhibitors, including donepezil, rivastigmine, galantamine, and tacrine, as well as the N-methyl-D-aspartate (NMDA) antagonist memantine, have been approved by the US Food and Drug Administration; however, they only provide temporary symptom relief [4]. There has been increasing research on neuroinflammation in AD, which is characterized by the presence of reactive astrocytes and activated microglial cells mainly around amyloid plaques. Neuroinflammation is crucially involved in the pathophysiology of AD [5]. Natural substances with anti-inflammatory effects have been investigated in studies on AD treatment; however, they have limited ability to cross the blood-brain barrier or are rapidly metabolized and eliminated [6]. Recent studies have demonstrated the anti-inflammatory effects of low-dose radiotherapy (LDRT) [7-9], which has shown efficacy against neuroinflammation in AD. Specifically, relatively low-to-moderate total doses of 9–10 Gy in 5 fractions have been shown to significantly reduce the amyloid plaque burden and/or tau staining in AD mouse models [10-13]. These previous studies applied a relatively low total dose of 10 Gy, which is lower than the 60 Gy generally used in cancer treatment; however, the dose per fraction remained similar to the conventional dose RT (1.8–2 Gy). Another research group has attempted treating AD using much lower RT doses. Yang et al. [14] revealed a proper RT dose and schedule for late-stage AD using 8- and 9-month-old 5xFAD mice, which is an established animal model for AD, by comparing the low total dose with a low single dose (5 × 0.6 Gy) and the low moderate total dose with conventional dose (5 × 2 Gy). They found that LDRT involving 5 fractions at 3 Gy could effectively reduce beta-amyloid in the brains of mice with AD and improve cognitive function. Further, the anti-inflammatory effect was confirmed by changes in cytokine levels. Therefore, we aimed to determine whether LDRT was effective in patients with AD.

Materials and Methods

1. Patients
The inclusion criteria were as follows: (1) men and women aged 60–85 years; (2) probable Alzheimer’s dementia according to the New Diagnostic Criteria for Alzheimer’s Disease (NIA-AA) [15]; (3) confirmation of amyloid plaque deposits on baseline amyloid positron emission tomography (PET); (4) mild-to-moderate AD with a Korean Mini-Mental State Examination 2nd edition (K-MMSE-2) score of 13–26; (5) Global Clinical Dementia Rating (CDR) score of 0.5–2 points; (6) ability to perform cognitive and other tests; (7) having an accompanying guardian (a family member or a trusted person who takes care of daily life) during the visits; (8) having provided written informed consent; and (9) having maintained the existing drug treatment for general dementia within > 3 months.

The exclusion criteria were as follows: (1) possible or probable vascular dementia according to the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) criteria [16]; (2) a history of other central nervous diseases as the main cause of dementia (cerebrovascular disease; structural or developmental malformation; epilepsy; infectious, degenerative, or infectious/demyelinating history) or presence of the corresponding evidence on brain MRI scans performed within the past 12 months or at screening; (3) uneducated or illiterate; (4) severe hearing and vision impairment that impeded efficacy evaluation; (5) abnormal test results for vitamin B12, syphilis serology, or thyroid stimulating hormone that may worsen or cause dementia; (6) a history of psychiatric diseases that may impede trial participation, including schizophrenia or bipolar disorder, or currently having severe depression (Geriatric Depression Score-Short Form [SGDS] ≥ 12); (7) a diagnosis of a malignant tumor within 5 years from the screening time; or (8) a history of brain irradiation for therapeutic intent.

2. Study design
After approval from the Institutional Review Board of Chungbuk National University Hospital (IRB No. 2021-04-011-007), this prospective, single-center, investigator-initiated pilot study was conducted to evaluate the safety and effectiveness of LDRT for AD. The study period was from June 2021 to June 2022, and a total of seven subjects were planned to be recruited. The patients underwent whole-brain irradiation involving six doses of LDRT (0.5 Gy). After the end of treatment, the patients underwent cognitive function tests and PET-CT follow-ups for efficacy evaluation (Fig. 1). The medication for AD treatment was maintained. Beyond 6 months follow-up, further visit will be continued through an outpatient of neurology department.

3. Radiotherapy
The patients underwent treatment planning computed tomography (CT) while immobilized. The clinical target volume (CTV) was measured within the whole brain. The planning target volume (PTV) was determined by expanding the CTV by 5 mm. The inferior border of the field was placed at the inferior endplate of the C1 vertebra (Fig. 2). The prescribed dose of the PTV for whole-brain RT was 3 Gy, 0.5 Gy/time, and three times/week. Regarding the planned optimization goals, > 95% of the PTV received the prescribed dose. A linear accelerator (LINAC) Versa HD (LEKTA, Stockholm, Sweden)
with low-dose-rate photons (6 MV, 100 MU/min) was used for treatment delivery.

4. Outcome measures
Neurocognitive function was evaluated using the Seoul Neuropsychological Screening Battery II (SNSB-II) at baseline as well as 3 and 6 months after the LDRT schedule. The primary outcome was the change in the CDR-sum of boxes (SB) score. The secondary outcomes were the change in the K-MMSE-2, z-score of each SNSB domain, Korean Instrumental Activities of Daily Living Scale (K-IADL), Barthel Index for Activities of Daily Living (ADL), SGDS, and Global Deterioration Scale (GDS). Moreover, the amyloid burden was measured at baseline and 3 months after LDRT.

5. Amyloid PET–CT acquisition and PET parameters
18F-florapronol scans were performed to quantitatively assess the amyloid burden before and 3 months after LDRT. For each PET–CT scan, a dose (mean ± standard deviation) of 379.5 ± 12.7 MBq of 18F-florapronol was intravenously injected; furthermore, PET–CT images were acquired from 30 to 60 minutes after injection using the GE Discovery STE 16 (cases 1 and 2) and GE Discovery MI Gen2 (cases 3, 4, and 5) scanners (GE Healthcare, Waukesha, WI, USA). Four brain regions (frontal, temporal, parietal, and occipital cortices) in each scan were automatically delineated using the MIM-neuro application (version 7.16, MIM Software Inc., Beachwood, OH, USA), and the standardized uptake value (SUV) for each region was obtained. Individual SUV ratios (SUVRs) were calculated as the ratio of the mean SUV of each region to the mean SUV of the reference region (cerebellum). The global SUVR was defined as the average SUVR of the four brain regions.

6. Safety evaluation
The safety and tolerability of LDRT were assessed at four time points (weekly during LDRT as well as 1 month, 3 months, and 6 months after completion of LDRT) using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

7. Data analysis
The Wilcoxon signed-rank test was used to analyze the total CDR-SB score as well as the scores for the SNSB domains, K-MMSE-2, CDR-GS, GDS, SGDS, K-IADL, and Barthel-ADL. Additionally, the amyloid burden was measured using 18F-florapronol PET/CT scans before and after LDRT. Statistical analyses were performed using the SPSS software version 24.0 for Windows (IBM Corp., Armonk, NY, USA).

8. Ethical approval and informed consent statements
This study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments or with the laws and regulations of the locality in which the research was conducted (whichever afforded greater protection to the individual). Written informed consent was provided by each patient, the patient’s representative, and by each participating caregiver.

Fig. 1. A schematic diagram of the study. PET-CT, positron emission tomography-computed tomography; SNSB, Seoul Neuropsychological Screening Battery; WBRT, whole-brain radiotherapy; f/u, follow-up.

Fig. 2. Beams eye view of whole brain radiotherapy.
Results

1. Patient population

We enrolled only five patients (all female) with mild-to-moderate AD because patients were no longer enrolled during the recruitment period. All patients completed LDRT and the 6 months of follow-up. Table 1 shows the baseline characteristics of the patients. Patients had a mean age of 71.8 years (range, 60 to 83 years) and mean years of education of 7.8 (range, 3 to 18 years). At baseline, all patients were only treated using acetylcholinesterase (AChE) inhibitors. The mean duration of illness and medication were 30.4 months (range, 8 to 62 months) and 29.2 months (range, 8 to 62 months), respectively. Three of the five patients were apolipoprotein E ε4 carriers.

Table 1. Demographic and baseline characteristics (n = 5)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
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</tr>
<tr>
<td>Sex</td>
<td>Female: 5</td>
</tr>
<tr>
<td></td>
<td>Male: 0</td>
</tr>
<tr>
<td>Education (yr)</td>
<td>7.8 (3–18)</td>
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<tr>
<td>Age at onset (yr)</td>
<td>68.2 (59–77)</td>
</tr>
<tr>
<td>Duration of medication (mo)</td>
<td>29.2 (8–62)</td>
</tr>
<tr>
<td>Duration of illness (mo)</td>
<td>30.4 (8–62)</td>
</tr>
<tr>
<td>Alzheimer’s disease medication used</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Medication (acetylcholinesterase inhibitor)</td>
<td>5</td>
</tr>
<tr>
<td>K-MMSE-2 score</td>
<td>21 (16–25)</td>
</tr>
<tr>
<td>CDR-GS</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>CDR-SB</td>
<td>4.7 (4–5.5)</td>
</tr>
<tr>
<td>GDS</td>
<td>4 (4–4)</td>
</tr>
<tr>
<td>K-IADL</td>
<td>4.5 (1–5)</td>
</tr>
<tr>
<td>SGDS</td>
<td>4.4 (1–8)</td>
</tr>
<tr>
<td>Apolipoprotein E ε4 carriers</td>
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<tr>
<td>Carriers</td>
<td>3</td>
</tr>
<tr>
<td>Non-carriers</td>
<td>2</td>
</tr>
<tr>
<td>Amyloid deposit on PET-CT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number.

K-MMSE-2, Korean Mini-Mental State Examination 2nd edition; CDR-GS, Clinical Dementia Rating—Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; GDS, Global Deterioration Scale; K-IADL, Korean-Instrumental Activities of Daily Living; SGDS, Short version of Geriatric Depression Scale; PET-CT, Positron emission tomography—computed tomography.

2. Patient #1

A 75-year-old woman complained of memory disturbance since the age of 73 years. She did not recognize places she had visited several times before. Additionally, she experienced problems with using public transportation by herself, cooking, and shopping. She had graduated from elementary school and was homozgyous for ε4 alleles. She had hypertension and a meningioma (0.8 cm) in the left parasagittal dura. She was on several medications, including donepezil (10 mg), choline alfoscerate (400 mg twice a day), amlodipine (5 mg), and alprazolam (0.125 mg). At baseline, the z-scores for SNB domains were as follows: attention, 1.52; language, -0.71; visuospatial function, -0.25; memory, -2.50; and frontal/executive function, -2.67. The scores for the other neuropsychological measures were as follows: K-MMSE-2, 24/30; SGDS, 8/15; K-IADL, 10/2; CDR, 1 (SB 5); and GDS, 4 (Tables 2, 3).

Just after LDRT, she complained of depressive mood due to impaired cognition; accordingly, vortioxetine 2.5 mg was added to her treatment regimen. At 3 months after LDRT, the donepezil dose was increased to 15 mg due to progressive memory impairment reported by her husband. Despite being more cheerful and participating more in group activities, the neuropsychological tests revealed progressive worsening in all domains except for the frontal and executive function, which showed a z-score improvement from -2.67 to -0.98 at 6 months. No adverse events occurred after the LDRT.

Table 2. Comparison of K-MMSE-2 before and after LDRT

<table>
<thead>
<tr>
<th>K-MMSE-2</th>
<th>Pre-LDRT</th>
<th>3 m after</th>
<th>6 m after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1</td>
<td>24</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Patient #2</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Patient #3</td>
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<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Patient #4</td>
<td>25</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>Patient #5</td>
<td>16</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

K-MMSE-2, Korean Mini-Mental State Examination 2nd edition; LDRT, low dose radiotherapy.

Table 3. Comparison of CDR-SB before and after LDRT

<table>
<thead>
<tr>
<th>CDR-SB</th>
<th>Pre-LDRT</th>
<th>3 m after</th>
<th>6 m after</th>
</tr>
</thead>
<tbody>
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<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Patient #2</td>
<td>5.0</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Patient #3</td>
<td>4.0</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Patient #4</td>
<td>4.0</td>
<td>4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Patient #5</td>
<td>5.5</td>
<td>8.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

CDR-SB, Clinical Dementia Rating-Sum of Box; LDRT, low dose radiotherapy.
3. Patient #2
A 74-year-old woman complained of progressive cognitive impair-ment for 2 years. While cooking, she ruined her meals by repeatedly adding salt. Her husband reported episodic memory impairment, including forgetting her daughter’s visit or important appointments. She was apathetic and had no interest in going out or cooking. She had been educated for 6 years and had worked as a farmer. Her mother and older sister also had dementia. She was a carrier of the ε2 and ε4 alleles.

At baseline, the z-scores for each SNSB domain were as follows: attention, -0.31; language, -0.46; visuospatial function, 0.79; memory, -3.31; and frontal/executive function, -0.08. The scores for the other neuropsychological measures were as follows: K-MMSE-2, 20/30; SGDS, 8/15; Barthel-ADL, 20/20; K-IADL, 8/2; CDR 1 (SB 5); and GDS 4 (Tables 2, 3). Her treatment regimen included donepezil (15 mg), choline alfoscerate (400 mg twice a day), and quetiapine (12.5 mg).

The patient completed LDRT without any adverse events. At 3 months after LDRT, she reported improvement in her chronic insomnia. Her husband reported amelioration of her jealousy episodes after LDRT, for example when he was helping neighbors. Further, her daughter reported improvement in recent memory about 6 months after LDRT. There were improvements in all the SNSB domains. Additionally, The K-MMSE-2 and SGDS scores improved from 20 to 23 and from 8 to 2, respectively.

4. Patient #3
An 83-year-old woman with memory impairment was followed up for 6 years in the Department of Neurology. She had been educated for 3 years and had homozygous ε3 alleles. Her medication regimen included donepezil (10 mg) and quetiapine (12.5 mg). Further, she was taking medication for hypertension.

At baseline, she showed impaired language and related functions, memory, and frontal/executive function. The z-scores for each SNSB domain were as follows: attention, 0.32; language and related function, -3.65; visuospatial function, 0; memory, -2.14; and frontal and executive function, -1.71. Moreover, the scores for the K-MMSE-2, SGDS, CDR (SB), and GDS scores were 20/30, 1/15, 1 (4.0), and 4, respectively (Tables 2, 3).

She complained of mild hair loss as an adverse event during LDRT; however, it improved after 6 months. At 3 post-LDRT months, she and her son reported an improvement in mood swings and memory. The CDR (SB) improved from 1 (4.0) to 1 (3.5) at 3 months follow-up. The z-scores for language and related functions, memory, and frontal executive functions improved to -2.56, -1.86, and -1.32, respectively at 6 months follow-up.

5. Patient #4
A 60-year-old woman with a master’s degree who worked as a nurse for 30 years complained of cognitive impairment for 2 years. She made mistakes in calculations and forgot where she placed her belongings. She had recently given up on going to another city by herself since she was worried about losing her way. Her grandmother and father had presented with dementia in their eighties. The patient was heterozygous for ε2/ε4 alleles. She was taking galantamine (8 mg) and fluoxetine (10 mg) due to complaints of depressive mood and loneliness.

At baseline, the z-scores for each SNSB domain were as follows: attention, -0.96; language and related function, -0.26; visuospatial function, -8.9; memory, -4.19; and frontal and executive function, -5.92. Moreover, her K-MMSE-2, SGDS, CDR (SB), and GDS scores were 25/30, 1/15, 1 (4), and 4, respectively (Tables 2, 3).

During LDRT, the patient complained of dizziness, headache, and nausea, which improved after treatment completion. She and her husband reported progressive aggravation of her memory and visuospatial function. She had difficulties solving puzzles, playing with blocks or distinguishing cardinal points. She developed severe depression between 3 and 6 months of follow-up evaluation.

At the 6-month follow-up, the K-MMSE-2, SGDS, CDR (SB), and GDS scores worsened to 19/30, 13/15, 1 (4.5), and 4, respectively. Visuospatial function and frontal executive function showed the most severe worsening, with the z-scores decreasing to -12.97 at 3 months and -24.56 at 6 months, respectively. Her visuospatial function could not be evaluated since she could not complete the Rey Complex Figure Copy task at the 6-month follow-up examination.

6. Patient #5
A 67-year-old woman experienced difficulties finding words and staying on topic for 7 years. She had graduated from elementary school and had homozygous ε2/ε3 alleles. She was taking donepezil (10 mg) and choline alfoscerate (400 mg) twice daily.

At baseline, the z-scores for each SNSB domain were as follows: attention, -2.65; language and related function, -6.52; visuospatial function, -2.06; memory, -4.10; and frontal and executive function, -4.58. Her K-MMSE-2, SGDS, CDR (SB), and GDS scores were 16/30, 3/15, 1 (5.5), and 4, respectively (Tables 2, 3).

At 6 months after LDRT, her husband reported worsened difficulty in finding words and newly developed fecal incontinence. She did not complete the Rey Complex Figure Copy task; accordingly, the visuospatial function and visual memory could not be evaluated. Her K-MMSE-2, CDR (SB), and GDS scores were aggravated to 11/30, 2 (SB 10), and 5, respectively.
7. Comparison of PET parameters before and after the LDRT

The mean interval between the PET/CT scans before and after LDRT was 101 ± 27.6 days. The mean global SUVRs before and after LDRT were 1.24 ± 0.11 and 1.27 ± 0.14, respectively. Although the global and regional amyloid burden showed an increasing tendency, there were no significant differences between the SUVRs before and after LDRT.

8. Subjective changes

Caregivers of two of five patients reported improved cognitive function and improved memory. For example, patient #3 was confused about going to her house in the apartment after being diagnosed with dementia, but after LDRT, she got better enough to find her house correctly. Then, she was able to take the bus to the grocery store by herself. And, patient #2 came to remember a song she had forgotten in the past, and her short-term memory improved, such as remembering something her husband went to pick up a while ago. Also, the mood of the patient improved to the point where she could joke with the other party.

9. Side effects

One patient complained of nausea (Grade II of CTCAE v5.0) during LDRT, which subsided after treatment. Another patient reported mild hair loss (Grade I of CTCAE v5.0) during LDRT, which also improved after the trial. No other adverse effects were observed.

Discussion and Conclusion

Our findings demonstrated the safety of LDRT in patients with mild-to-moderate AD; however, its efficacy remains unclear. In a previous case report, an 81-year-old woman with severe AD showed partial restoration of cognitive function and appetite after exposure to several 40-mGy brain CT scans for 2 years [17]. A subsequent pilot study was conducted to confirm the effects of brain CT on patients with severe AD. Four patients with AD underwent three standard brain CT scans, with the first scan emitting a dose of 80 mGy and the subsequent two scans emitting a dose of 40 mGy. Three of the four patients showed qualitative and quantitative improvements in cognition, communication, and behavior [18]. Although this pilot study had several limitations, including a relatively small sample size and lack of placebo groups, it demonstrated the potential for LDRT to treat AD.

Another group recently launched a clinical trial on LDRT for early AD defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria using a LINAC [19]. This study included patients whose florbetapir and FDG PET findings were consistent with AD. Five patients were treated with low-dose whole-brain RT (10 Gy in 5 fractions); among them, four patients showed stability to improvement in the MMSE-2, naming, learning, and memory scores; stability in executive function, processing, mood, and quality of life; and stability to possible improvement in PET imaging. The protocol of 10 Gy in 5 fractions was based on the results of a previous preclinical study [20]. The RT dose was a relatively low total dose of 10 Gy, however, the dose per fraction remained the same as the conventional dose RT (1.8–2 Gy). Notably, several countries such as Germany, extensively apply low total doses with low doses per fraction (total dose 3–6 Gy, single dose <1 Gy) to treat inflammatory-degenerative disorders [9]. There is a mutual relationship between RT and the immune system, which is highly dependent on the dose and quality of radiation. A high total dose of conventional-dose RT (total dose 50–70 Gy, single dose ≥1.8 Gy) generally used to treat cancer exacerbates inflammation [21]; conversely, LDRT can be used to control various inflammatory processes and has shown anti-inflammatory properties [22]. Based on the results, the German Society of Radiation Oncology recommends single fraction doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy/series for LDRT for painful degenerative skeletal disorders [9]. Accordingly, there has been interest in the efficacy of LDRT for improving inflammation and symptoms in patients with AD. Yang et al. [14] compared the effectiveness of LDRT with 10 Gy and 3 Gy in 5 fractions in an AD mouse model and confirmed that both radiation doses effectively improved cognitive function. The most effective radiation dose for treating AD remains unclear. However, if the treatment effect is the same, it would be advantageous to extensively reduce the radiation dose.

The mechanisms through which LDRT regulates AD remain unclear. In AD, soluble amyloid-β 42, which is abnormally cleaved from an amyloid precursor protein, aggregates into oligomers such as dimers, trimers, pentamers, and fibril to form insoluble amyloid plaques [23]. Soluble amyloid-β 42 oligomers mainly induce neurotoxic effects. In the asymptomatic preclinical stage of AD, microglia clear amyloid-β; however, soluble amyloid-β is overproduced in the more advanced stages, which binds to the surface receptor of microglia and triggers microglial activation, leading to the M1 phenotype [24]. Upon exposure of microglia to stressors such as radiation, the activated M1 microglia release pro-inflammatory cytokines including interleukin-1 (IL-1) beta, IL-6, and tumor necrosis factor-alpha, which contribute to neuronal damage and secondary injury, limiting the utility of the elimination of soluble amyloid-β [25,26]. However, there is increasing evidence that LDRT is neuroprotective rather than an inflammatory stressor. Notably, LDRT has been shown to switch the M1/M2 ratio in the hip-
pocampus of 5xFAD mice. M1-typed and M2-typed microglia produce pro- and anti-inflammatory cytokines, respectively [27]. Specifically, patients with AD present with increased M2-typed microglia in early-stage AD and M1-typed microglia in late-stage AD [28]. Kim et al. [29] reported that lipopolysaccharide- and LDRT-treated BV-2 microglial cells showed a significant increase in the M2 phenotypic marker CD206 compared with LPS- and sham-treated BV-2 cells. Finally, the effect of LDRT on M2 polarization was confirmed by increased TREM2 expression in LPS-induced BV-2 cells.

Although the underlying mechanism remains unclear, numerous cellular and animal studies have reported that low-dose ionizing irradiation (LDIR) promotes longevity, neurogenesis, and cognition while decreasing ROS production [14,20,30,31]. However, the effect of LDRT on microglia in humans remains unclear; moreover, the current understanding of radiation hormesis is poor.

It has been reported that taking donepezil, which is most commonly used for Alzheimer’s disease, reduces the MMSE score by an average of 2.5 points per year [32]. Although the follow-up period was as short as 6 months, the present study showed maintained or improved MMSE scores in two out of five patients. In addition, in a recently published study of lecanemab, it was reported that the cognitive decline was delayed by 27% in the experimental group compared to the control group [33]. In our study, cognitive function was improved in 40% of patients, which is quite encouraging, and it is expected that further research will be worthwhile.

This study has several limitations. First, the sample size was too small to determine the efficacy of LDRT. Second, there was no control group. Patients with AD present with cognitive deterioration even with drug treatment. Even if drug treatment slows the rate of cognitive decline, it cannot effectively treat AD. A control group is required to determine whether the addition of LDRT slows down the rate of cognitive decline. Third, the follow-up period (6 months) was too short to evaluate the efficacy of LDRT. Given the long-term progression of AD, follow-up periods of at least 7 months to 4.5 years are required to confirm the reduction of amyloid deposits or symptomatic relief in non-CNS amyloidosis. Contrastingly, our follow-up period of 6 months may have been too short to observe clinical benefits possibly mediated by anti-inflammatory effects. However, since AD is a progressive neurodegenerative disease with rapid progression in old age [34], a practical observation period is required that does not offset the cognitive benefit of intervention.

Currently, six clinical studies into the use of LDIR for the treatment of AD are ongoing according to clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02769000, NCT05635968, NCT03352258, NCT02359864, NCT03597360, and NCT00599469). Our research team is participating in one of the studies (NCT04203121). In the future, studies on various factors that can affect prognosis, such as stage of AD (mild/moderate/severe), apolipoprotein E genotype, RT energy level (kVp, MeV), RT beam emission type, RT field, total dose, fractional size, intrafractional interval, interfractional interval, dose rate, etc., should be conducted.

In conclusion, at 6 months after LDRT, neurological improvement was seen in 20% of patients. One of our five patients with AD showed a temporary improvement in CDR-SB; moreover, two patients showed stable improvement in the K-MMSE score 2. Since there were no serious side effects above grade 3, LDRT seems to be tolerable in patients with AD. This report is an interim analysis. We are currently under follow-up and will conduct cognitive function tests after 12 months after LDRT (IRB No. 2022-11-022). However, to determine the effect of LDRT in patients with mild-to-moderate AD, a large-scale randomized controlled trial with a long follow-up period of > 1 year is required.

**Statement of Ethics**

This study was approved by the Institutional Review Board of Chungbuk National University Hospital (IRB No. 2021-04-011-007).

**Conflict of Interest**

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

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**Author Contributions**

Conceptualization, Kim A, Seo YS, Yoo MY. Funding acquisition, Kim WD, Seo YS. Investigation and methodology, Kim A. Seo YS, Moon H, Lee JH, Kim C. Project administration, Kim WD, Seo YS. Resources, Seo YS. Supervision, Seo YS, Kim WD. Writing of the original draft, Kim A. Seo YS, Moon H, Lee JH. Writing of the review and editing, Seo YS. Software, Seo YS, Moon H. Validation, Kim A. Seo YS, Moon H, Lee JH. Formal analysis, Kim A. Seo YS, Moon H, Lee JH, Kim C. Data curation, Seo YS, Moon H. Visualization, Seo YS, Kim A.

**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.
References


Radiotherapy trend in elderly hepatocellular carcinoma: retrospective analysis of patients diagnosed between 2005 and 2017

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³Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea

Purpose: To report the trends of radiotherapy in the management of elderly patients with hepatocellular carcinoma (HCC).

Materials and Methods: We retrospectively reviewed patients who entered HCC registry of Samsung Medical Center between 2005 and 2017. Patients who were 75 years or older at the time of registration were defined as elderly. They were categorized into three groups based on the year of registration. Radiotherapy characteristics were compared between the groups to observe differences by age groups and period of registration.

Results: Out of 9,132 HCC registry patients, elderly comprised 6.2% (566 patients) of the registry, and the proportion increased throughout the study period (from 3.1% to 11.4%). Radiotherapy was administered to 107 patients (18.9%) in elderly group. Radiotherapy utilization in the early treatment process (within 1 year after registration) has rapidly increased from 6.1% to 15.3%. All treatments before 2008 were delivered with two-dimensional or three-dimensional conformal radiotherapy, while more than two-thirds of treatments after 2017 were delivered with advanced techniques such as intensity-modulated radiotherapy, stereotactic body radiotherapy, or proton beam therapy. Overall survival (OS) of elderly was significantly worse than younger patients. However, for patients who received radiotherapy during the initial management (within one month after registration), there was no statistically significant difference in OS between age groups.

Conclusion: The proportion of elderly HCC is increasing. Radiotherapy utilization and adoption of advanced radiotherapy technique showed a consistently increasing trend for the group of patients, indicating that the role of radiotherapy in the management of elderly HCC is expanding.

Keywords: Hepatocellular carcinoma, Aged, Radiotherapy

Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide [1]. In South Korea, primary liver cancer was the second most common cause of cancer-related death in 2020 and the number one cause of death among people aged 40–50 years [2]. Approximately 75% of all primary liver cancers are hepatocellular carcinoma (HCC) [3]. The crude incidence rate of HCC in South Korea has slowly decreased over a 10-year period (from 2008 to 2018) [4]. However, the age-standardized incidence rates in those aged ≥80 years have significantly increased [5]. Elderly patients tend to have multiple comorbidities and are considered vulnerable to surgical and/or systemic treatment related complications [6,7]. According to the vital
Radiotherapy trend in elderly HCC

statistics of South Korea, a 75-year-old man in 2020 is expected to live an additional 11.6 years, and a 75-year-old woman in 2020 is expected to live an additional 14.7 years [8], indicating the need for appropriate treatment for elderly patients with HCC. However, while there is a consistent need for appropriate treatment guidelines for elderly patients with HCC due to the above-mentioned issues, there is still a lack of recommendations focusing on these patients [2,9].

Radiotherapy in the management of HCC was limited due to the radiosensitive nature of background normal liver parenchyma [10,11]. However, with advancements in radiotherapy techniques, the role of radiotherapy in the management of HCC has changed dramatically over the last few decades. With the aid of improved image guidance, conformal delivery techniques, and various radiotherapy modalities, radiotherapy for HCC has resulted in high local control rates with relatively low toxicity in multiple clinical trials [12-16].

Though multiple studies report that the role of radiotherapy in the management of HCC is changing [2,13,17] and that radiotherapy is equally safe and effective for elderly patients [18-20], there is a current lack of an overall review of how radiotherapy is administered for the management of elderly patients with HCC in the real world. Therefore, in this study, we aimed to report how radiotherapy utilization for the management of these patients has changed over time.

Materials and Methods

1. Study population

This retrospective study used the prospectively collected registry data of patients with newly diagnosed, previously untreated HCC at Samsung Medical Center. The diagnosis of HCC was confirmed histologically or clinically, based on the guidelines of the Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) [21-23]. The HCC registry collected the baseline clinical characteristics of the patients, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, hypertension, diabetes, Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLC) stage, and initial treatment method. Details of the HCC registry have been previously described [24,25]. The data of patients registered between 2005 and 2017 were used for this study.

This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (No. 2021-12-093-001). Written informed consent was waived due to the retrospective nature of the study.

2. Assessments

We investigated whether radiotherapy was utilized in the subsequent HCC treatment process. Medical records between January 2005 and December 2022 were reviewed. Following radiotherapy characteristics were collected: treatment aim (curative vs. palliative), target lesion (intrahepatic vs. other), radiotherapy timing (during initial management vs. during the treatment course), and radiotherapy technique—two-dimensional radiotherapy (2D-RT) vs. three-dimensional conformal radiotherapy (3D-CRT) vs. intensity-modulated radiotherapy (IMRT) vs. stereotactic body radiotherapy (SBRT) vs. proton beam therapy (PBT). All of the radiotherapy sessions were counted individually if the patient underwent multiple sessions of radiotherapies. SBRT or high-dose irradiation to intrahepatic lesions, and high-dose radiotherapy in addition to transarterial chemoembolization (TACE) were regarded as curative aim radiotherapy. TACE is considered as palliative treatment, and TACE plus radiotherapy is also generally considered as a treatment option beyond curative intent [26]. However, the treatment option is frequently administered in real clinical practice when surgical or ablative procedures are infeasible, and several studies have reported comparable results to hepatic resection or radiofrequency ablation (RFA) [27-31]. Therefore, our institution provides TACE plus high-dose radiotherapy as a viable alternative treatment option for patients who are ineligible for hepatic resection or RFA [32]. With the above-mentioned reasons, in this study, we have regarded high-dose radiotherapy in addition to TACE as curative aim radiotherapy. Radiotherapy for management of symptomatic metastasis, and relief of portal vein thrombosis were regarded as palliative aim radiotherapy. Radiotherapy in initial management was defined as radiotherapy utilized within one month after registration. Radiotherapy during the early treatment process was defined as radiotherapy utilized within one year after registration.

The patients were categorized based on two factors: the age of the patients and the year of registration. First, patients were grouped as younger (<75 years) or elderly (≥75 years) or very elderly (≥80 years) based on their ages at the time of registration. Second, as the KLCA-NCC HCC practice guideline was updated in 2009, 2014, 2018, and 2022 [21,22-23], patients were categorized into three different groups based on the year of the practice guideline update: Period 1 (registered between 2005 and 2009), Period 2 (registered between 2010 and 2014), and Period 3 (registered between 2015 and 2017).

3. Statistical analysis

Variables are presented as medians with interquartile ranges or frequencies with percentages as appropriate. Differences in variables between the groups were compared using t-test or chi-square test.
Overall survival (OS) was analyzed using the Kaplan-Meier method, and comparisons of the survivals were performed with the log-rank test. A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Inc., Armonk, NY, USA).

Results

1. HCC registry
Among the 9,132 patients entered into the HCC registry during the study period, 8,566 (93.8%) were younger, 566 (6.2%) were elderly, and 152 (1.7%) were very elderly. Though the overall proportion of the elderly and very elderly was low, the incidence increased significantly throughout the study period: from 3.1% (18 patients) to 11.4% (91 patients) for the elderly and from 0.5% (3 patients) to 3.8% (30 patients) for the very elderly. The annually registered number of patients with HCC and the proportion of elderly and very elderly are illustrated in Fig. 1.

The patients’ clinical characteristics differed significantly between the age groups. The elderly patients had a significantly higher proportion of females, HCC with non-viral etiology, diabetes, hypertension, worse ECOG performance status, and high BCLC stage. Details of the clinical characteristics are summarized in Table 1.

2. Radiotherapy in the HCC registry
In the subsequent HCC treatment process, 2,572 patients (28.2%) underwent 3,746 radiotherapy sessions, with 2,465 patients (28.8%) from the younger group undergoing 3,604 radiotherapy sessions and 107 patients (18.9%) from the elderly group undergoing 142 radiotherapy sessions. A significantly higher proportion of patients in the elderly group received radiotherapy with a curative aim with advanced radiotherapy techniques compared to the younger group. However, the proportion of patients receiving radiotherapy for intrahepatic lesion and radiotherapy in initial treatment was significantly lower for the elderly patients. Details of the radiotherapy are summarized in Table 2.
Table 1. Baseline clinical characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort (n = 9,132)</th>
<th>Younger (n = 8,566)</th>
<th>Elderly (n = 566)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 (51–65)</td>
<td>56 (50–63)</td>
<td>77 (76–80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>7,302 (80.0)</td>
<td>6,936 (81.0)</td>
<td>366 (64.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,830 (20.0)</td>
<td>1,630 (19.0)</td>
<td>200 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBV</td>
<td>6,704 (73.4)</td>
<td>6,576 (76.8)</td>
<td>128 (22.6)</td>
<td></td>
</tr>
<tr>
<td>HBV + HCV</td>
<td>113 (1.2)</td>
<td>105 (1.2)</td>
<td>8 (1.4)</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>868 (9.5)</td>
<td>707 (8.3)</td>
<td>161 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>566 (6.2)</td>
<td>496 (5.8)</td>
<td>70 (12.4)</td>
<td></td>
</tr>
<tr>
<td>NBNC</td>
<td>841 (9.2)</td>
<td>649 (7.6)</td>
<td>192 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>26 (0.3)</td>
<td>20 (0.2)</td>
<td>6 (1.1)</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>14 (0.2)</td>
<td>13 (0.2)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>1,938 (21.2)</td>
<td>1,744 (20.4)</td>
<td>194 (34.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,194 (78.8)</td>
<td>6,822 (79.6)</td>
<td>372 (65.7)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>2,649 (29.0)</td>
<td>2,315 (27.0)</td>
<td>334 (59.0)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,483 (71.0)</td>
<td>6,251 (73.0)</td>
<td>232 (41.0)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0–1</td>
<td>8,974 (98.3)</td>
<td>8,449 (98.6)</td>
<td>525 (92.8)</td>
<td></td>
</tr>
<tr>
<td>2 or higher</td>
<td>158 (1.7)</td>
<td>117 (1.4)</td>
<td>41 (7.2)</td>
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<tr>
<td>BCLC stage</td>
<td></td>
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<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0</td>
<td>1,749 (19.2)</td>
<td>1,659 (19.4)</td>
<td>90 (15.9)</td>
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</tr>
<tr>
<td>A</td>
<td>3,805 (41.7)</td>
<td>3,565 (41.6)</td>
<td>240 (42.4)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>993 (10.9)</td>
<td>926 (10.8)</td>
<td>67 (11.8)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2,360 (25.8)</td>
<td>2,221 (25.9)</td>
<td>139 (24.6)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>225 (2.5)</td>
<td>195 (2.3)</td>
<td>30 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh classification</td>
<td></td>
<td></td>
<td></td>
<td>0.660</td>
</tr>
<tr>
<td>A</td>
<td>7,848 (85.9)</td>
<td>7,359 (85.9)</td>
<td>489 (86.4)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1,127 (12.3)</td>
<td>1,057 (12.3)</td>
<td>70 (12.4)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>157 (1.7)</td>
<td>150 (1.8)</td>
<td>7 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).
HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C hepatitis; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; N/A, not applicable.

3. Radiotherapy trend of elderly patients in the HCC registry

Fig. 2 illustrates the radiotherapy utilization rate over time with patients categorized based on age and the year of registration. The rates of the elderly group are shown in a solid line, and the rates of the younger group are shown in a dotted line. The radiotherapy utilization rate has gradually increased over time (red to orange to blue line) regardless of the age group. The overall utilization rate of the elderly group was lower than that of the younger group. However, the gap between the age groups has been narrowing over time. It was also to note that the radiotherapy utilization rate in the elderly is rapidly increasing in the early HCC treatment process, radiotherapy utilized within one year after registration, from 6.1% in Period 1 to 15.3% in Period 3. The utilization rates are summarized in Table 3.

The trends of radiotherapy utilization in the elderly are illustrated in Fig. 3. The number of patients receiving radiotherapy (Fig. 3A) and the proportion of respective radiotherapy techniques (Fig. 3B) are shown based on the year of radiotherapy. Radiotherapy utilization in these elderly patients has increased overtime. While only two radiotherapy sessions were performed in 2006, 30 radiotherapy sessions were performed in 2017. After peak radiotherapy utilization was observed in 2017, the number of radiotherapy utilization gradually decreased afterwards due to the population of the
Table 2. Radiotherapy characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entire cohort (n = 9,132)</th>
<th>Younger (n = 8,566)</th>
<th>Elderly (n = 566)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT during HCC treatment</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>2,572 (28.2)</td>
<td>2,465 (28.8)</td>
<td>107 (18.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,560 (71.8)</td>
<td>6,101 (71.2)</td>
<td>459 (81.1)</td>
<td></td>
</tr>
<tr>
<td>Intrahepatic RT</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>1,959 (21.5)</td>
<td>1,876 (21.9)</td>
<td>83 (14.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,173 (78.5)</td>
<td>6,690 (78.1)</td>
<td>483 (85.3)</td>
<td></td>
</tr>
<tr>
<td>RT in initial treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Yes</td>
<td>514 (5.6)</td>
<td>495 (5.8)</td>
<td>19 (3.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8,618 (94.4)</td>
<td>8,071 (94.2)</td>
<td>547 (96.6)</td>
<td></td>
</tr>
<tr>
<td>RT aim</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Curative</td>
<td>953 (25.4)</td>
<td>900 (25.0)</td>
<td>53 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>2,793 (74.6)</td>
<td>2,704 (75.0)</td>
<td>89 (62.7)</td>
<td></td>
</tr>
<tr>
<td>RT technique</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2D-RT</td>
<td>326 (8.7)</td>
<td>324 (8.0)</td>
<td>2 (1.4)</td>
<td></td>
</tr>
<tr>
<td>3D-CRT</td>
<td>2,208 (58.9)</td>
<td>2,136 (59.3)</td>
<td>72 (50.7)</td>
<td></td>
</tr>
<tr>
<td>IMRT</td>
<td>353 (9.4)</td>
<td>339 (9.4)</td>
<td>14 (9.9)</td>
<td></td>
</tr>
<tr>
<td>SBRT</td>
<td>367 (9.8)</td>
<td>344 (9.5)</td>
<td>23 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Proton</td>
<td>492 (13.1)</td>
<td>461 (12.8)</td>
<td>31 (21.8)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).

RT, radiotherapy; HCC, hepatocellular carcinoma; 2D-RT, two-dimensional; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.

Fig. 2. Radiotherapy utilization rates of the different patient groups. The elderly groups are shown in solid lines and the younger groups are shown in dotted lines. Patients registered between 2005 and 2009 are categorized as Period 1 (red), between 2010 and 2014 as Period 2 (orange), and between 2015 and 2017 as Period 3 (blue).
Fig. 3. Radiotherapy utilization in elderly HCC registry patients. (A) The number of radiotherapies is shown in stacked column chart, with curative intent shown in blue bar and palliative intent shown in yellow bar. (B) The proportion of utilized radiotherapy techniques is shown as 100% stacked column chart. As this study is based on patients registered between 2005 and 2017, radiotherapies after 2018 are shown in a translucent box. HCC, hepatocellular carcinoma; RT, radiotherapy; PBT, proton beam therapy; SBRT, stereotactic body radiotherapy; IMRT, intensity-modulated radiotherapy; 3D CRT, three-dimensional conformal radiotherapy; 2D RT, two-dimensional radiotherapy.

Table 3. Radiotherapy utilization rate (%)

<table>
<thead>
<tr>
<th>Years after diagnosis</th>
<th>Elderly</th>
<th>Younger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>1 year</td>
<td>6.1</td>
<td>6.7</td>
</tr>
<tr>
<td>2 years</td>
<td>7.6</td>
<td>9.8</td>
</tr>
<tr>
<td>5 years</td>
<td>12.1</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Current study. As this study is based on patients who entered HCC registry between 2006 and 2017, patients diagnosed after 2018 were not included, resulting in a decreased number of radiotherapy utilization after 2018. The proportion of patients receiving curative aim radiotherapy changed during the study period. While only 15.6% of radiotherapies in Periods 1 and 2 were curative aim (7 out of 45 radiotherapy sessions), 47.4% of radiotherapies in Period 3 and after were curative (46 out of 97 radiotherapy sessions). Utilized radiotherapy techniques have also changed dramatically during the study period. While all of the patients treated before 2008 were managed with either 2D-RT or 3D-CRT, more than two-thirds of the patients who underwent radiotherapy after 2017 were managed with advanced radiotherapy techniques, such as IMRT, SBRT, or PBT.

Fig. 4. Kaplan-Meier overall survival curves of elderly patients in the HCC registry, categorized based on the year of registration. Patients registered between 2005 and 2009 are categorized as Period 1 (red), between 2010 and 2014 as Period 2 (orange), and between 2015 and 2017 as Period 3 (blue). HCC, hepatocellular carcinoma.
4. OS of elderly patients in HCC registry

The OS of the elderly patients in the HCC registry is illustrated in Fig. 4. Periods 1 and 2 did not differ significantly, with a respective 5-year OS of 33.6% and 30.2% (p = 0.991). However, OS significantly improved in Period 3 compared to the previous two groups, with a 5-year OS of 53.5% (Period 1 vs. 3, p < 0.001; Period 2 vs. 3, p = 0.011).

We also compared the OSs of the elderly and younger patients in the same registration period. As illustrated in Fig. 5, OS was significantly worse for elderly patients throughout the study period. The respective 5-year OSs were 33.6% versus 48.6% (p < 0.001) for Period 1, 30.2% versus 55.2% (p < 0.001) for Period 2, and 53.5% versus 69.7% (p < 0.001) for Period 3.

Discussion and Conclusion

This study shows the current trend of radiotherapy in the management of elderly patients with HCC in our institution. The proportion of these patients was continuously increasing. The radiotherapy utilization rate also increased during the study period, especially during the early HCC treatment process. The proportion of advanced radiotherapy techniques also increased over time. Our results demonstrate the changing role and increasing utilization of radiotherapy for the management of elderly HCC.

The reason for the increased proportion of radiotherapy utilization seems to be due to the following factors. Compared to the past, radiotherapy-related hepatic toxicity is better understood [10,11,33]. Based on the understandings and concrete evidences, liver constraints are becoming more detailed with consideration of radiation dose, fraction size, irradiated liver volume, and hepatic function [34,35]. The introduction of IMRT, SBRT, and particle beam radiotherapy, and improvements in image-guided radiotherapy has led to more precise and conformal radiotherapy available [17]. It has become possible to achieve the complex and tight dose constraints consistently, leading to widening the indications for radiotherapy, resulting in increasing trend of radiotherapy utilization for HCC.

Elderly patients with HCC are known to have several distinct characteristics compared to younger patients [5,36-38]. First, they are reported to have a higher proportion of female patients, due to longer life expectancy of women [39,40]. Second, the proportion of patients with HBV infection is lower, and HCV infection is higher for these patients [38]. Third, the proportion of patients with non-viral etiology is higher [38,41], which is likely to be associated with the increasing incidence of non-alcoholic fatty liver disease-related HCC in elderly patients [42,43]. Our findings are in line with other previously reported studies: female (35.3% vs. 19.0%), HBV (22.6% vs. 76.8%), HCV (28.4% vs. 8.3%), NBNC

![Fig. 5. Kaplan-Meier overall survival curves of elderly and younger patients in the HCC registry, categorized based on the year of registration. The elderly groups are shown in solid line, and younger groups are shown in dotted line. Patients registered between 2005 and 2009 are categorized as Period 1 (red), between 2010 and 2014 as Period 2 (orange), and between 2015 and 2017 as Period 3 (blue). HCC, hepatocellular carcinoma.](https://doi.org/10.3857/roj.2023.00353)

Table 4. Summary of retrospective studies of radiotherapy for elderly patients with hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (yr)</th>
<th>Radiotherapy</th>
<th>Local control (%)</th>
<th>Overall survival (%)</th>
<th>Toxicity ≥ grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teraoka et al.</td>
<td>117</td>
<td>≥ 75 (n = 54)</td>
<td>SBRT</td>
<td>3-yr, 98.1</td>
<td>3-yr, 63.9</td>
<td>7.4 (n = 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 75 (n = 63)</td>
<td>SBRT</td>
<td>3-yr, 98.4</td>
<td>3-yr, 67.7</td>
<td>6.3 (n = 4)</td>
</tr>
<tr>
<td>Jang et al.</td>
<td>83</td>
<td>≥ 75</td>
<td>SBRT</td>
<td>5-yr, 90.1</td>
<td>5-yr, 40.7</td>
<td>3.6 (n = 3)</td>
</tr>
<tr>
<td>Iwata et al.</td>
<td>71</td>
<td>≥ 80</td>
<td>PBT</td>
<td>2-yr, 88.0</td>
<td>2-yr, 76.0</td>
<td>0 (n = 0)</td>
</tr>
</tbody>
</table>

SBRT, stereotactic body radiotherapy; PBT, proton beam therapy.
As shown in Fig. 5, there was significant OS difference between elderly and younger patients throughout the study period. Several factors may have influenced the survival differences. First, elderly patients usually have multiple comorbidities, representing a hard-to-manage, complex group of patients [9,44]. They are considered to be more vulnerable to treatment-related complications [6,37]. The elderly patients in current study had significantly higher proportion of comorbidities, and this could have led to worse survival of the elderly group (Table 1). Second, there are no clear prospective evidence or treatment guidelines for elderly patients with HCC currently. This may lead to the undertreatment of medically fit patients, and the overtreatment of medically unfit patients, affecting survival of the patients [9].

However, the role of radiotherapy in elderly patients with HCC is not fully established, and there are only a few retrospective studies available. Teraoka et al. [18] evaluated the safety and efficacy of SBRT for elderly patients with HCC. They compared clinical outcomes between the elderly group (aged 75 years or older) and the younger group (aged younger than 75 years) and reported that there was no statistically significant difference in clinical outcomes between the groups. Jang et al. [19] also investigated the role of SBRT for elderly patients with HCC. They retrospectively reviewed patients 75 years or older who underwent SBRT for HCC. The 5-year local tumor control rate was 90.1%, and OS was 40.7% with minimal treatment-related toxicity, which was comparable with the clinical outcomes in all age group [45]. Iwata et al. [20] investigated the efficacy and safety of image-guided PBT for elderly patients with HCC, aged 80 years or older. They report 2-year OS and local control of 88% and 76%, respectively. Toxicity was minimal with no reduction in quality of life during or after PBT. The results of the studies are summarized in Table 4. We also observed that though the OS of the elderly patients was worse compared to that of the younger patients, the OS of patients who received radiotherapy during the initial management was not different between the age groups (Fig. 5). The finding potentially indicates that radiotherapy in the management of elderly patients with HCC is as effective as in the management of younger patients with HCC. Taken together, radiotherapy for the elderly patients with HCC seems to be equally effective and safe as for the younger patients with HCC. However, the results should be taken with caution as the studies are retrospective in nature with relatively small sample sizes.

There were several limitations in this study. First, this study is based on registry data from a single institution in an HBV-endemic country. The patient population and treatment policy of our institution may not be identical to those of other institutions or countries. Second, we did not perform a qualitative analysis of radiotherapy, such as radiotherapy dose, treatment outcomes, or toxicity. Third, as the study population is the HCC registry patients registered between 2005 and 2017. The results may not accurately reflect how currently diagnosed patients are being treated. However, though the limitations, we believe that the current study adequately presents the changing trend of radiotherapy in the management of elderly patients with HCC in actual clinical practice.

In conclusion, there was a consistent trend in increased incidence and proportion of elderly patients with HCC during the study period. With the aid of advancements in radiotherapy techniques, the role and utilization of radiotherapy in the management of elderly patients with HCC has increased. The role of radiotherapy in the management of elderly HCC is expected to further increase in the future.

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (No. 2021-12-093-001). Written informed consent was waived due to the retrospective nature of the study.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, Park HC. Investigation and methodology, Park HC; Bae BK; Yu JI. Project administration, Park HC. Resources, Park HC; Bae BK; Yu JI. Supervision, Park HC. Writing of the original draft, Park HC; Bae BK. Writing of the review and editing, Park HC; Bae BK; Yu JI; Goh MJ; Paik YH. Formal analysis, Park HC; Bae BK; Yu JI. Data curation, Park HC; Bae BK; Yu JI; Goh MJ; Paik YH. Visualization, Park HC; Bae BK; Yu JI.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.
References


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Nationwide changes in radiation oncology travel and location of care before and during the COVID–19 pandemic

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Purpose: Patients with cancer are particularly vulnerable to coronavirus disease (COVID). Transportation barriers made travel to obtain medical care more difficult during the pandemic. Whether these factors led to changes in the distance traveled for radiotherapy and the coordinated location of radiation treatment is unknown.

Materials and Methods: We analyzed patients across 60 cancer sites in the National Cancer Data Base from 2018 to 2020. Demographic and clinical variables were analyzed for changes in distance traveled for radiotherapy. We designated the facilities in the 99th percentile or above in terms of the proportion of patients who traveled more than 200 miles as “destination facilities.” We defined “coordinated care” as undergoing radiotherapy at the same facility where the cancer was diagnosed.

Results: We evaluated 1,151,954 patients. There was a greater than 1% decrease in the proportion of patients treated in the Mid-Atlantic States. Mean distance traveled from place of residence to radiation treatment decreased from 28.6 to 25.9 miles, and the proportion traveling greater than 50 miles decreased from 7.7% to 7.1%. At “destination facilities,” the proportion traveling more than 200 miles decreased from 29.3% in 2018 to 24% in 2020. In comparison, at the other hospitals, the proportion traveling more than 200 miles decreased from 1.07% to 0.97%. In 2020, residing in a rural area resulted in a lower odds of having coordinated care (multivariable odds ratio = 0.89; 95% confidence interval, 0.83–0.95).

Conclusion: The first year of the COVID pandemic measurably impacted the location of U.S. radiation therapy treatment.

Keywords: Radiation Oncology, COVID-19, Access to health care

Introduction

The coronavirus disease 2019 (COVID-19) pandemic had an unprecedented impact on all aspects of medical care. For cancer patients, the medical impact of the pandemic extended beyond direct infection by covid. Patients with cancer are particularly vulnerable to COVID and experience the dual impact of cancer and its treatment as well as an increased risk of infection [1]. As a result of this risk, the early response from many radiation oncology facilities was to reduce or delay radiation treatment visits [2]. Furthermore, transportation barriers made travel to obtain medical care more difficult during the pandemic [3]. Given the repeated nature of most radiation treatments, travel and transportation issues are particularly relevant for patients undergoing radiotherapy [4]. Whether these factors led to changes in where radiation oncology treatment occurred, and the distance traveled by patients for ra-
Changes in radiation oncology travel

The location of radiation oncology care may also reflect overall cancer care coordination, since cancer patients can be diagnosed at one healthcare facility and treated at another. For example, patients can often present to a relatively distant academic tertiary center for workup and diagnosis but can be treated at a radiation facility closer to home. Alternatively, patients can be diagnosed at their community hospital but elect to travel further to a higher volume radiation facility for treatment. Since half of all cancer patients undergo radiation therapy at some point in their cancer care, coordination of radiation oncology care is a critical issue for study [5]. This is particularly important for patients living in rural environments, as multiple locations of care and distance traveled may be exacerbated given the geographic maldistribution of radiation oncology practice in these areas [6]. Whether the COVID-19 pandemic has impacted the coordinated location of radiation therapy receipt is unknown.

The aims of this study are therefore twofold. First, we aim to evaluate the distance traveled by patients undergoing radiotherapy in 2020 (which we define as having happened during the COVID-19 pandemic) versus 2018 and 2019. Second, we aim to evaluate whether there were changes in the proportion of patients who underwent radiation at the same facility that diagnosed their cancer in 2020 versus 2018 and 2019. For the purposes of our study, if patients underwent radiation at the same facility that diagnosed their cancer, we will consider this “coordinated care.”

Materials and Methods

1. Description of the data
The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, that collects hospital registry data from over 1,500 accredited facilities. The database accounts for approximately 72% of U.S. cancer patients [7]. The NCDB participant user file (PUF) contains de-identified patient-level data from CoC accredited programs. For this study, disease sites were obtained for analysis encompassing the 60 most common primary disease sites for radiotherapy (Supplementary Table S1). The data includes patients diagnosed through 2020.

2. Sample construction
We analyzed only patients from 2018–2020 to evaluate the most immediate pre and during-pandemic years available. Sixty cancer sites were included (Supplementary Table S1). We excluded patients who did not have radiation treatment as recorded in RAD_LOCATION_OF_RX variable. This resulted in 1,151,954 patients (Fig. 1).

3. Construction of variables
Ten independent variables of interest were selected a priori to evaluate for association with the dependent variables: age of patients, race (White, Black, non-White other), sex, residence in a metropolitan area, residence in an area with highest quartile of median income, type of insurance, status of insurance, type of treating facility, number of Charlson Comorbidities, and stage of cancer.

Metropolitan areas were defined as counties with populations of more than 250,000 people. The highest income quartile was defined in the NCDB using the 2016 American Community Survey (ACS) data spanning 2012–2016 and indicated an area median household income of ≥ $63,333.

First, for patients who received radiation at the diagnosing facility, CROWFLY, the “great circle” distance in miles between the patient’s residence and the hospital that reported the case, was used as a surrogate for travel distance. Of note, distance from place of residence to radiation treatment facility was not able to be measured if a different facility from the facility that reported the cancer to the NCDB. Patients who received radiotherapy at a facility different from the diagnosing facility were excluded from the analysis of travel distance to radiotherapy centers.

Second, radiation care was designated as “coordinated” if all radiation treatment including initial and boost therapy was delivered at the diagnosing facility. All other radiation was otherwise considered not “coordinated.” RAD_LOCATION_OF_RX, which identifies the location where radiation therapy was administered during the first course of treatment, was therefore used as a surrogate for coordinated care (Supplementary Table S2). Specifically, if RAD_LOCATION_OF_RX indicated all radiation treatment occurred at the reporting facility, we designated this “coordinated care.” Care that took place in multiple locations, or radiation therapy that happened at a facility that was not the reporting facility, was not considered coordinated.
4. Statistical analysis

1) Travel distance

Descriptive statistics were performed. Travel distance was dichotomized to distant versus close travel by whether the great circle distance between the patient’s residence and radiotherapy facility was greater than 50 miles [8]. Univariate and multivariate logistic regression was performed to assess independent variables associated with distant travel. Variables were assessed for correlation using a pairwise Pearson correlation matrix. Only age and insurance status approached a strong (r = 0.48) correlation. Given lack of significant correlation, all variables were included in the multivariable analysis. Weak correlation was seen between living in a metropolitan area and an area of high average income (r = -0.28). All other correlation coefficients were < 0.20.

To evaluate the association between year of diagnosis and travel on the facilities with the highest volume of patients coming from far distances, we first counted the number of patients who got treated with radiation at the same facility that reported the cancer, who traveled more than 200 miles for treatment. We designated the facilities in the 99th percentile or above in terms of the proportion of patients who traveled more than 200 miles as “destination facilities.” We measured the decrease in the proportion of patients who traveled more than 200 miles in 2020 versus 2019 in these “destination facilities” versus all other facilities.

2) Coordinated care

Coordinated care broadly means coordinated information sharing and care management between healthcare providers in diagnosis and treatment [9]. Coordinated care has been shown to improve patient survival, reduce readmission, and patient satisfaction [10-12]. Furthermore, coordinated cancer care has been investigated in the NCDB in the same manner as our study for colorectal and pancreatic cancer, showing improved overall survival [13,14]. We assume that care given by a radiation oncology facility that is also the same facility that diagnosed the cancer will have “coordinated care” through coordinated information sharing and patient management.

Descriptive statistics were performed. Univariate and stepwise multivariate logistic regression was performed to assess independent variables associated with coordinated care. To compare year over year changes, we compared the mean travel distance in 2020 compared to 2019, and in 2019 to 2018 using a t-test. We also compared the percent of patients who traveled more than 50 miles in 2020 compared to 2019, and in 2019 compared to 2018 using the chi-squared test of proportions. This was performed for all patients (and thus was analyzing patient travel to their facility of diagnosis) as well as only those who underwent radiation at the same facility that diagnosed their cancer (and so measured distance to radiation facility in these patients). We did not perform a formal trend test as we only had three time points (2018, 2019, and 2020). Given the large number of patients, we used p < 0.001 as the threshold for statistical significance.

Due to the number of disease sites involved, a subset of lung, breast, and prostate cancer was evaluated as the most common solid tumors. Cervical cancer was also evaluated as an example of particularly complex radiotherapy care as treatment often requires coordinated external beam treatment and brachytherapy. Due to the number of primary tumors evaluated (encompassing 319 unique ICD-O-3 primary tumor codes), we did not evaluate the impact of different primary tumor types on travel distance or coordinated care. Specific evaluation of selected primary tumor types is the focus of future work.

All statistical analysis was performed with STATA 17.0 (StataCorp, College Station, TX, USA). Given the large size of the evaluated dataset, statistical significance was a priori defined as p < 0.001.

Results

We evaluated 1,151,954 patients who underwent radiotherapy from 2018–2020. The absolute number of patients in our analysis declined from 2019 to 2020, from 407,525 patients in 2019 to 345,068 in 2020. This was a significant deficit and other investigators have noted this large decline as well [15].

Characteristics of patients undergoing radiation therapy were generally similar throughout 2018–2020 (Table 1). Characteristics that changed more than 1% from 2018–2019 to 2020 included a decrease in the proportion of patients treated in the Mid-Atlantic (NJ, NY, PA), decrease in the proportion of patients with private insurance or managed care, decrease in the proportion of patients treated at an academic or comprehensive cancer center, and an increase in the proportion treated at a community cancer center.

Mean distance traveled from place of residence to the facility that reported the cancer to the NCDB decreased from 28 miles in 2018 to 2020 (Table 2). The proportion traveling greater than 50 miles decreased from 9.1% to 8.6%. Mean distance traveled from place of residence to radiation treatment (if it was the same facility that reported the cancer) decreased from 28.6 to 25.9 miles, and the proportion traveling greater than 50 miles decreased from 7.7% to 7.1% (Table 3).

Given the large size of the database, all variables were significantly associated with odds of travel more than 50 miles in 2020 in univariable logistic regression. In our multivariable logistic regression model, age, sex, metropolitan versus urban versus rural residence, Race, geographic area, income, and type of diagnosing
Table 1. Demographics and characteristics of patients and reporting institutions (unit: %)

<table>
<thead>
<tr>
<th></th>
<th>2018 (n = 399,361)</th>
<th>2019 (n = 407,525)</th>
<th>2020 (n = 345,068)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>64.0</td>
<td>64.2</td>
<td>64.2</td>
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<tr>
<td>Median (interquartile range)</td>
<td>65 (57–72)</td>
<td>65 (57–72)</td>
<td>65 (57–73)</td>
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</tr>
<tr>
<td>Male</td>
<td>40.2</td>
<td>40.3</td>
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<tr>
<td>Female</td>
<td>59.8</td>
<td>59.7</td>
<td>60.2</td>
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<td>Area of residence category</td>
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<tr>
<td>Metropolitan</td>
<td>82.4</td>
<td>82.4</td>
<td>82.4</td>
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<tr>
<td>Urban</td>
<td>13.3</td>
<td>13.5</td>
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<tr>
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<td>1.7</td>
<td>1.7</td>
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<tr>
<td>Unknown/unrecorded</td>
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<td>2.4</td>
<td>2.1</td>
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<tr>
<td>Race</td>
<td></td>
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<td></td>
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<tr>
<td>White</td>
<td>82.4</td>
<td>82.2</td>
<td>82.2</td>
</tr>
<tr>
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<td>11.8</td>
<td>11.7</td>
</tr>
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<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Asian/Pacific islander</td>
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<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
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<td>2.2</td>
</tr>
<tr>
<td>Location treated</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>New England (CT, MA, ME, NH, RI, VT)</td>
<td>6.1</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Middle Atlantic (NJ, NY, PA)</td>
<td>15.1</td>
<td>15.1</td>
<td>14.0</td>
</tr>
<tr>
<td>South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, WV)</td>
<td>21.5</td>
<td>21.4</td>
<td>21.9</td>
</tr>
<tr>
<td>East North Central (IL, IN, MI, OH, WI)</td>
<td>17.2</td>
<td>17.2</td>
<td>17.7</td>
</tr>
<tr>
<td>East South Central (AL, KY, MS, TN)</td>
<td>6.7</td>
<td>6.5</td>
<td>6.7</td>
</tr>
<tr>
<td>West North Central (IA, KS, MN, MO, ND, SD)</td>
<td>7.5</td>
<td>7.4</td>
<td>7.9</td>
</tr>
<tr>
<td>West South Central (AR, LA, OK, TX)</td>
<td>7.1</td>
<td>7.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Mountain (AZ, CO, ID, MT, NM, NV, UT, WY)</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Pacific (AK, CA, HI, OR, WA)</td>
<td>11.3</td>
<td>11.5</td>
<td>11.1</td>
</tr>
<tr>
<td>Not available</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Average income of area of residence (US dollars)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50,353</td>
<td>32.8</td>
<td>32.7</td>
<td>32.5</td>
</tr>
<tr>
<td>&gt; 50,353</td>
<td>51.6</td>
<td>51.3</td>
<td>51.1</td>
</tr>
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<td>16.0</td>
<td>16.4</td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not insured</td>
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<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Private insurance/managed care</td>
<td>38.9</td>
<td>38.0</td>
<td>37.8</td>
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<td>Medicaid</td>
<td>7.7</td>
<td>7.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Medicare</td>
<td>48.2</td>
<td>48.7</td>
<td>49.2</td>
</tr>
<tr>
<td>Other government</td>
<td>2.2</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Insurance status unknown</td>
<td>1.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Type of diagnosing facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community cancer program</td>
<td>6.7</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Comprehensive community cancer program</td>
<td>36.0</td>
<td>36.2</td>
<td>37.3</td>
</tr>
<tr>
<td>Academic/research program (includes NCI designated CCC)</td>
<td>34.8</td>
<td>34.6</td>
<td>33.4</td>
</tr>
<tr>
<td>Integrated network cancer program$^{11}$</td>
<td>19.1</td>
<td>18.8</td>
<td>19.1</td>
</tr>
<tr>
<td>Unknown/unrecorded</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>4.6</td>
<td>4.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Stage I</td>
<td>33.5</td>
<td>34.2</td>
<td>34.1</td>
</tr>
<tr>
<td>Stage II</td>
<td>17.9</td>
<td>17.7</td>
<td>17.2</td>
</tr>
</tbody>
</table>

(Continued to the next page)
facility were all associated significantly with travel more than 50 miles (Table 4). Patient-specific variables such as stage and comorbidity were less associated with travel more than 50 miles.

Destination hospitals were those in the top 1% of proportion of patients traveling more than 200 miles. At those hospitals, the proportion traveling more than 200 miles decreased from 29.3% and 28% in 2018 and 2019 to 24% in 2020. In comparison, at the other hospitals, the proportion traveling more than 200 miles decreased from 1.07% and 1.13% to 0.97%.

Regarding coordinated radiation treatment in 2020, all variables were again associated with coordinated treatment on univariate logistic regression. In our multivariate logistic regression model, independent variables associated with geography and facility type were associated with coordinated care. Individual characteristics such as race, comorbidity, and cancer stage were less obviously associated (Table 5). While residing in a rural area had a much higher odds of traveling more than 50 miles (multivariable odds ratio [OR] = 20.9; 95% confidence interval [CI], 19.2–22.8), it also had a lower odds of having coordinated care (multivariable OR = 0.89; 95% CI, 0.83–0.95). In contrast, though patients who were treated at academic research programs including the National Cancer Institute (NCI) designated cancer centers had a much higher odds of

Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>2018 (n = 399,361)</th>
<th>2019 (n = 407,525)</th>
<th>2020 (n = 345,068)</th>
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<tbody>
<tr>
<td>Stage III</td>
<td>17.8</td>
<td>17.6</td>
<td>17.3</td>
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<tr>
<td>Stage IV</td>
<td>15.3</td>
<td>15.1</td>
<td>15.6</td>
</tr>
<tr>
<td>Occult (lung only)</td>
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<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>AJCC staging not applicable</td>
<td>7.8</td>
<td>7.6</td>
<td>7.9</td>
</tr>
<tr>
<td>AJCC stage group unknown</td>
<td>3.1</td>
<td>3.1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Comorbidity score

<table>
<thead>
<tr>
<th>Comorbidity score</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>74.7</td>
<td>74.4</td>
<td>73.7</td>
</tr>
<tr>
<td>1</td>
<td>15.5</td>
<td>15.4</td>
<td>15.8</td>
</tr>
<tr>
<td>2</td>
<td>5.4</td>
<td>5.5</td>
<td>5.7</td>
</tr>
<tr>
<td>≥ 3</td>
<td>4.4</td>
<td>4.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Place of radiation treatment relative to reporting facility

<table>
<thead>
<tr>
<th>Place of radiation treatment relative to reporting facility</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>All radiation treatment at this facility&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74.6</td>
<td>75.0</td>
<td>74.8</td>
</tr>
<tr>
<td>Regional treatment at this facility, boost elsewhere</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Boost radiation at this facility</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>All radiation treatment elsewhere</td>
<td>24.6</td>
<td>24.2</td>
<td>24.4</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; CCC, comprehensive cancer center; AJCC, American Joint Committee on Cancer.
<sup>a</sup>Facilities belonging to an organization that owns a group of facilities that offer integrated and comprehensive cancer care services and is overseen by a centralized governance structure/board and CEO.
<sup>b</sup>These patients designated as “coordinated care.”

Table 2. Distance traveled between place of residence and reporting hospital

<table>
<thead>
<tr>
<th>Distance traveled (miles)</th>
<th>Distance traveled (miles)</th>
<th>≥ 50 miles travel (%)</th>
<th>With missing travel data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median (IQR)</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>30.4</td>
<td>10.7 (4.9–24.1)</td>
<td>9.1</td>
</tr>
<tr>
<td>2019</td>
<td>30.7</td>
<td>10.9 (4.9–24.2)</td>
<td>9.1</td>
</tr>
<tr>
<td>2020</td>
<td>28.0</td>
<td>10.8 (4.9–23.8)</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Table 3. Distance traveled between place of residence and radiation center (if the same as reporting hospital)

<table>
<thead>
<tr>
<th>Distance traveled (miles)</th>
<th>≥ 50 miles travel (%)</th>
<th>With missing travel data (%)</th>
<th>≥ 1,000 miles travel (%)</th>
<th>With missing travel data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median (IQR)</td>
<td>2018</td>
<td>2019</td>
</tr>
<tr>
<td>2018</td>
<td>28.6</td>
<td>9.9 (4.5–21.7)</td>
<td>7.7</td>
<td>1.54</td>
</tr>
<tr>
<td>2019</td>
<td>28.7</td>
<td>10.0 (4.6–21.8)</td>
<td>7.7</td>
<td>1.46</td>
</tr>
<tr>
<td>2020</td>
<td>25.9</td>
<td>9.9 (4.6–21.3)</td>
<td>7.1</td>
<td>1.18</td>
</tr>
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</table>

https://doi.org/10.3857/roj.2023.00164
Table 4. In patients who underwent radiation at the diagnosing facility, univariate and multivariate logistic regression for variables associated with >50 miles traveled, in the year 2020

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>Wald p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (continuous variable)</td>
<td>0.993 (0.992–0.994)</td>
<td>&lt; 0.0001</td>
<td>0.992 (0.990–0.994)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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</tr>
<tr>
<td>Female (vs. male)</td>
<td>0.71 (0.69–0.74)</td>
<td>&lt; 0.0001</td>
<td>0.84 (0.80–0.87)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Area of residence category</td>
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<td>10.38 (9.91–10.87)</td>
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<td>Rural</td>
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<tr>
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<tr>
<td>Black</td>
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<td>0.45 (0.42–0.48)</td>
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<td>Asian/Pacific islander</td>
<td>0.36 (0.32–0.41)</td>
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<tr>
<td>East North Central (IL, IN, MI, OH, WI)</td>
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<td>4.68 (4.14–5.29)</td>
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<td>&lt; 0.0001</td>
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<td>1 (Reference)</td>
<td>&lt; 0.0001</td>
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<td>&lt; 0.0001</td>
<td>0.57 (0.55–0.60)</td>
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<td></td>
</tr>
<tr>
<td>Not insured</td>
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<td>1 (Reference)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Private insurance/managed care</td>
<td>0.86 (0.78–0.96)</td>
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<tr>
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<td>0.95 (0.82–1.10)</td>
<td>0.483</td>
</tr>
<tr>
<td>Medicare</td>
<td>0.84 (0.76–0.83)</td>
<td>&lt; 0.0001</td>
<td>1.29 (1.12–1.47)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Other government</td>
<td>1.45 (1.28–1.65)</td>
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<td>0.012</td>
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<tr>
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<td>1 (Reference)</td>
<td>&lt; 0.0001</td>
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<tr>
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<td>&lt; 0.001</td>
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<tr>
<td>Academic/research program (includes NCI designated CCC)</td>
<td>4.87 (4.42–5.35)</td>
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<td>22.6 (20.3–25.3)</td>
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<td>Integrated network cancer program</td>
<td>1.64 (1.47–1.81)</td>
<td>&lt; 0.0001</td>
<td>4.89 (4.35–5.51)</td>
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<tr>
<td>Stage</td>
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<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>0.54 (0.49–0.60)</td>
<td>&lt; 0.0001</td>
<td>0.64 (0.56–0.72)</td>
<td>&lt; 0.001</td>
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<td>1 (Reference)</td>
<td>&lt; 0.0001</td>
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<td>&lt; 0.0001</td>
<td>1.10 (1.04–1.17)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Stage III</td>
<td>1.19 (1.14–2.25)</td>
<td>&lt; 0.0001</td>
<td>1.02 (0.96–1.08)</td>
<td>0.510</td>
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<tr>
<td>Stage IV</td>
<td>1.39 (1.33–1.45)</td>
<td>&lt; 0.0001</td>
<td>1.11 (1.04–1.17)</td>
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<tr>
<td>Occult (lung only)</td>
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(Continued to the next page)
### Table 4. Continued

<table>
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<th>Univariate</th>
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<tbody>
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<td></td>
<td>OR (95% CI)</td>
<td>Wald p-value</td>
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<td>AJCC stage group unknown</td>
<td>1.44 (1.33–1.57)</td>
<td>&lt; 0.001</td>
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<td>Comorbidity score</td>
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<tr>
<td>1</td>
<td>1.06 (1.02–1.11)</td>
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<td>0.10</td>
</tr>
<tr>
<td>≥ 3</td>
<td>0.92 (0.85–0.99)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

NCI, National Cancer Institute; CCC, comprehensive cancer center; AJCC, American Joint Committee on Cancer; OR, odds ratio; CI, confidence interval.

<sup>a</sup>Facilities belonging to an organization that owns a group of facilities that offer integrated and comprehensive cancer care services and is overseen by a centralized governance structure/board and CEO.

### Table 5. Univariate and multivariate logistic regression for variables associated with coordinated care, in the year 2020

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<thead>
<tr>
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<th>Univariate</th>
<th>Multivariate</th>
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</thead>
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<td></td>
<td>OR (95% CI)</td>
<td>Wald p-value</td>
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<td>Sex</td>
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<tr>
<td>Female (vs. male)</td>
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<tr>
<td>Area of residence category</td>
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<td>&lt; 0.0001</td>
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<tr>
<td>Metropolitan</td>
<td>1 (Reference)</td>
<td></td>
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<tr>
<td>Urban</td>
<td>0.96 (0.94–0.98)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Rural</td>
<td>0.92 (0.87–0.98)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>White</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.31 (1.28–1.35)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Native American</td>
<td>0.97 (0.86–1.10)</td>
<td>0.035</td>
</tr>
<tr>
<td>Asian/Pacific islander</td>
<td>0.82 (0.79–0.85)</td>
<td>0.312</td>
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<td>Other/unrecorded</td>
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<tr>
<td>Location treated</td>
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<td>&lt; 0.0001</td>
</tr>
<tr>
<td>New England (CT, MA, ME, NH, RI, VT)</td>
<td>1 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Middle Atlantic (NJ, NY, PA)</td>
<td>1.42 (1.36–1.47)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, WV)</td>
<td>1.01 (0.98–1.05)</td>
<td>0.015</td>
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<td>East North Central (IL, IN, MI, OH, WI)</td>
<td>1.56 (1.50–1.62)</td>
<td>&lt; 0.0001</td>
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<td>East South Central (IL, KY, MS, TN)</td>
<td>1.09 (1.05–1.14)</td>
<td>&lt; 0.0001</td>
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<tr>
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<td>1.05 (1.00–1.09)</td>
<td>&lt; 0.0001</td>
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<td>West South Central (AR, LA, OK, TX)</td>
<td>0.77 (0.74–0.80)</td>
<td>&lt; 0.0001</td>
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<td>Mountain (AZ, CO, ID, MT, NM, NV, UT, WY)</td>
<td>1.52 (1.45–1.60)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Pacific (AK, CA, HI, OR, WA)</td>
<td>0.77 (0.74–0.80)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average income of area of residence (US dollars)</td>
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<td>&lt; 0.0001</td>
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<tr>
<td>&lt; 50,353</td>
<td>1 (Reference)</td>
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</tr>
<tr>
<td>&gt; 50,353</td>
<td>0.89 (0.87–0.91)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Private insurance/managed care</td>
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<td>&lt; 0.0001</td>
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<tr>
<td>Medicaid</td>
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<td>0.454</td>
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<tr>
<td>Medicare</td>
<td>1.09 (1.02–1.15)</td>
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<tr>
<td>Other government</td>
<td>1.51 (1.39–1.63)</td>
<td>&lt; 0.0001</td>
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(Continued to the next page)
### Table 5. Continued

<table>
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<th>Univariate</th>
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<tbody>
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<td></td>
<td>OR (95% CI)</td>
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<tr>
<td>Stage II</td>
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<td>Stage III</td>
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<tr>
<td>Stage IV</td>
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<tr>
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<td>1.05 (1.03–1.07)</td>
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<td>2</td>
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<tr>
<td>≥ 3</td>
<td>1.16 (1.12–1.20)</td>
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</tbody>
</table>

NCI, National Cancer Institute; CCC, comprehensive cancer center; AJCC, American Joint Committee on Cancer; OR, odds ratio; CI, confidence interval.

a) Facilities belonging to an organization that owns a group of facilities that offer integrated and comprehensive cancer care services and is overseen by a centralized governance structure/board and CEO.

Changes in radiation oncology travel

We also performed univariate and multivariate logistic regression for patients diagnosed in 2018–2019 (Supplementary Table S3). These factors were broadly similar to patients diagnosed in 2020 with the exception that patients with Medicaid were no longer significantly less likely than those who were uninsured to have coordinated care. As well, in 2018–2019, integrated network cancer programs were not less likely to undergo coordinated care compared to the reference of the community cancer program, whereas in 2020 they were less likely to undergo coordinated care.

In regards to travel, for patients diagnosed in 2018–2019, the Mid-Atlantic States were more likely to have greater travel distance compared to New England, whereas in 2020 that difference was not statistically significant (Supplementary Table S4). Again, Medicaid patients in 2020 were equally likely to travel as those who were uninsured, whereas in 2018–2019 they were more likely to travel > 50 miles for care.

Patients were statistically significantly less likely to travel more than 50 miles in 2019 compared to 2020. Furthermore, the mean travel distance was statistically significantly lower in 2020 compared to 2019. This was true for all patients in relation to their diagnosing facilities, as well as patients in relation to their radiation treatment facility (if it was the same as their diagnosing facility). There were no statistically significant differences between 2018 and 2019.

Finally, the percent of patients with lung, breast, and prostate cancer traveling more than 50 miles are reported in Table 6. Generally, patients with breast, prostate and lung cancer were less likely to travel more than 50 miles for treatment compared to all cancers (6.7%, 8.8%, and 9.1%, respectively, vs. 10.1% in 2020). Lung and prostate cancer patients were more likely to receive coordinated care in all years, whereas breast cancer patients were less likely (80.3%, 83.8%, and 70.4%, respectively, vs. 74.8% for all cancers in 2020). Cervical cancer patients were both more likely to travel more than 50 miles (13.8% in 2020 and 15.9% in 2018–2019), and also less likely to have coordinated care (69.2% in 2020 and 68.3% in 2018–2019).

https://doi.org/10.3857/roj.2023.00164
### Table 6. Percent traveling more than 50 miles or receiving coordinated care by selected primary tumor type

<table>
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<tr>
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<th>All cancers</th>
<th>Lung</th>
<th>Breast</th>
<th>Prostate</th>
<th>Cervix</th>
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<tr>
<td></td>
<td>%</td>
<td>p-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>%</td>
<td>p-value&lt;sup&gt;a&lt;/sup&gt;</td>
<td>%</td>
</tr>
<tr>
<td>2020</td>
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<tr>
<td>Travel &gt; 50 miles</td>
<td>10.1</td>
<td>9.1</td>
<td>&lt;0.001</td>
<td>6.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Coordinated care</td>
<td>74.8</td>
<td>80.3</td>
<td>&lt;0.001</td>
<td>70.4</td>
<td>&lt;0.001</td>
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<tr>
<td>2018–2019</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travel &gt; 50 miles</td>
<td>10.7</td>
<td>9.3</td>
<td>&lt;0.001</td>
<td>7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coordinated care</td>
<td>74.8</td>
<td>80.0</td>
<td>&lt;0.001</td>
<td>69.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Chi-squared test for proportion (vs. all other cancers).

### Discussion and Conclusion

Though the proportions of patients traveling large distances and receiving coordinated radiation decreased only slightly from 2018 through 2020, the Mid-Atlantic States and academic centers had the greatest proportional decrease in patients radiated overall. Demographic, geographic, and facility level variables such as age, race, population density, and type of center were associated with greater travel, whereas clinical characteristics such as stage and comorbid illness were less associated. Centers who had a high proportion of patients traveling long distances for treatment experienced the greatest proportional decrease in those same patients in 2020 compared to 2018 and 2019. However, for the vast majority of radiation treatment centers, there was a minimal relative decline in the proportion of patients traveling long distances for diagnosis or radiation treatment.

These findings indicate that “destination” radiation oncology centers and academic centers experienced the greatest decrease in patient volume during the pandemic, and these patients were likely instead treated at radiation centers closer to a patient’s place of residence. Besides the expected financial implications corresponding to fluctuations in patient load, these changes may impact individual clinical care, as well. Multiple studies have shown that treatment at an academic center is associated with improved survival in a variety of types of cancer [16-20]. Moreover, a number of analyses have also demonstrated a survival benefit from being treated at a high-volume center [21-23]. Logically, higher volume may improve skill and proficiency among providers, leading to improved care. It follows that declines in the number of patients treated could eventually erode the clinical advantages at academic and destination centers, which are often high-volume facilities. While the relatively small changes we have detected are unlikely to cause significant changes in the short-term, these trends and their impact should continue to be closely monitored over time.

The changes in distance traveled may reflect the broader economic impact of the COVID-19 pandemic. For example, during the pandemic the poverty rate rose from 10.5% to 13.6% from 2019 to 2020 despite federal aid programs, resulting in an estimated 9.8 million people descending into poverty [24]. There was a reduction in available childcare, with over 70% of childcare arrangements canceled or reduced by August 2020, had disproportionate impact on low-income families [24]. At the same time, COVID-19 disrupted general access to health care with particular impact on low-income Black and Hispanic households, leading to delay of non-emergent care [25]. Preventative healthcare including cancer screenings experienced a sharp decrease in the early months of the pandemic, with incomplete rebound [26]. Given the unprecedented impact of the pandemic on national economic well-being and healthcare access, it is not surprising that our analysis reflected a decline in travel for radiation treatment.

Importantly, we found that distance traveled was associated with many socio-economic factors and less associated with disease specific factors. This is consistent with work showings socio-economic factors influence travel access to cancer care [27]. Furthermore, it is possible that we underestimated the impact of socio-economic factors on travel distance, as those with the most severe socio-economic barriers may not have received radiation at all.

We found that the common cancers of breast, prostate, and lung primary site were less likely to travel more than 50 miles than all cancers together. We hypothesize that more rare cancers or those cancers with more complex management could potentially move patients to travel longer distances whereas these relatively common cancers were readily treated at closer cancer centers. We also found that while lung and prostate cancer patients were more likely to receive coordinated care in all years, breast cancer patients were less likely (compared to all cancers) to receive coordinated care. This finding is in contradiction to conventional wisdom that reduced travel results in more coordinated care. However, it is also possible that physicians at diagnosing centers may attempt to alleviate patient travel burden by referring patients to providers closer to home, which may both reduce travel burden but also reduce coordination of care [28]. Why this would be unique to breast cancer
Changes in radiation oncology travel and location for these patients. Due to the number of primary tumors evaluated (encompassing 319 unique ICD-O-3 primary tumor codes), we did not evaluate the impact of different primary tumor types on travel distance or coordinated care. Specific evaluation of selected primary tumor types is the focus of future work.

Strengths of this study include the large size of our sample, including over a million patients and wide variety of cancer sites included. This allows for a nationwide assessment of how the pandemic impacted huge numbers of patients and facilities. Continued longitudinal studies are necessary to evaluate how travel and coordinated care changed as the COVID-19 pandemic evolved in the United States.

In conclusion, the proportion of patients treated in Middle Atlantic States with private insurance, at comprehensive cancer centers, decreased in the first year of the COVID-19 pandemic. Travel distance also declined, especially at facilities that had high levels of distant travelers in the pre-pandemic period. Further work should focus on the continued impact of the pandemic in subsequent years, and the impact of the pandemic on multidisciplinary coordination of care.

Statement of Ethics

This study used publicly available data and was exempt from institutional review.

Conflict of Interest

There are no conflicts of interest related to this work. Outside of this work, Dr. Yu reports research funding, speaking and consulting fees from Pfizer/Myovant, consulting fees from Boston Scientific, and Speaking fees from RefleXion Medical.

Funding

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Author Contributions

Conceptualization, Investigation and methodology, and writing of the original draft: De Leo AN, Giap F, Culbert MM, Drescher N, Brisson RJ, Cassidy V, Augistin EM, Casper A, Yu JB. Formal analysis: Yu JB. Writing of the review and editing: De Leo AN, Giap F, Culbert MM, Drescher N, Brisson RJ, Cassidy V, Augistin EM, Casper A, Horowitz DH, Cheng SK, Yu JB.
Data Availability Statement

NCDB data is publicly available for US Commission on Cancer (CoC) affiliated institutions.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00164.

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24. Winston P. COVID-19 and economic opportunity: unequal effects on economic need and program response [Internet]. Washington,


Introduction

The proportion of circulating immune cells might play an essential role in the treatment of patients with brain tumors. Numerous studies demonstrating effects of radiation therapy (RT) on hematological variables have been conducted mostly for high-grade glioma. These patients usually received concurrent radiotherapy with chemotherapy and required high doses of steroids [1-3].

Neutrophil-to-lymphocyte ratio (NLR) is known as a significant prognosis marker of solid tumors [4]. A systemic review evaluating 100 studies of 40,559 solid tumor patients has reported that the median cutoff for NLR is 4 and that NLR above this cutoff value is associated with a worse overall survival (OS) [4]. High NLR levels are also correlated with shorter OS and progression-free survival (PFS) of patients with high-grade glioma [1-3].

Elevated NLR reflects either neutrophilia, lymphopenia, or both.
Lymphocytes play an important role in the tumor environment and infections [6]. They are highlight sensitive to radiation. Severe treatment-related lymphopenia (<500 cells/mm\(^3\)) is related to worse survival of patients with newly diagnosed solid tumors [7].

In this study, we focused on low-grade brain tumors to rule out impacts of chemotherapy and high dose of steroid use. Changes of NLR, neutrophil counts, and lymphocytes counts were evaluated. Significant factors influencing such changes were determined. We also examined effects of radiation therapy on circulating immune cells and identified significant factors in order to reduce possible RT-induced immunotoxicity.

Materials and Methods

1. Patients

Patients diagnosed with the World Health Organization (WHO) grade I or II low-grade brain tumors who received brain RT between 2007 and 2020 were included. The following eligibility criteria were used to select the study population: (1) those aged 18 years or more, (2) those who had complete blood count (CBC) data within 1 week of beginning and ending RT, and (3) those who were not exposed to chemotherapy. We excluded patients who received high dose of steroid (daily dexamethasone 5 mg or higher dose) during the treatment or patients who did not complete planned RT. A total of 41 patients were eligible and included for this study. All patients did not have any active infectious or auto-immune disease which might affect CBC. The median age of patients at diagnosis was 52 years (range, 18 to 83 years). Brain tumor pathology was mainly meningioma (n = 20; 48.8%) and low-grade gliomas (n = 12; 29.3%) (Table 1). This study was approved by the Institutional Review Board of Seoul St. Mary’s Hospital (No. KC22RISI0266). The informed consent was waived.

2. Protocol of CBC and DVH analysis

Absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC) were collected before starting the RT (baseline) and within one week before finishing the RT (post-treatment). Changes of ANC, ALC, and NLR between baseline and post-treatment were calculated. The NLR was calculated by dividing ANC by ALC. Each of planning target volume (PTV) size was collected. Dosimetric factors such as maximum dose (D\(_{\text{max}}\)), minimum dose (D\(_{\text{min}}\)), mean dose (D\(_{\text{mean}}\)), and brain volume receiving ≥ 5 Gy (V\(_{5}\), V\(_{10}\), V\(_{20}\), V\(_{25}\), V\(_{30}\), V\(_{35}\), V\(_{40}\), and V\(_{45}\)) were extracted from brain dose-volume histogram (DVH).

3. Radiotherapy

RT was mainly used as an adjuvant treatment after operation. In the present study, 39 (96%) of 41 patients received RT for adjuvant purpose. One (2%) patient received RT for radical aim and one (2%) received it for salvage aim after recurrence. The median delivered total dose of RT was 5,400 cGy (range, 4,680 to 6,000 cGy). The fraction size of RT was mainly 180 cGy (n = 35; 85.4%) or 200 cGy (n = 5, 12.2%). Only one patient received hypo-fractionation with daily dose of 240 cGy. The duration of RT was median 42 days (range, 28 to 55 days). The three-dimensional conformal RT (3D-CRT) group consisted of 19 patients and the intensity-modulated radiotherapy (IMRT) group had 22 patients. IMRT was performed with Helical Tomotherapy (Accuray, Sunnyvale, CA, USA).

The target volume was defined as follows: gross tumor volume (GTV) was defined in patients with residual or recurrent gross disease in pre-radiotherapy brain MRI. Clinical target volume (CTV)
was defined as postoperative cavity in all patients with addition of T2 high-signal intensity lesion in low-grade brain tumor patients. PTV was defined CTV plus 5-mm margin in 3D-CRT patients, and 3-mm margin in IMRT patients. IMRT was performed with daily mega-voltage CT image-guided radiotherapy (IGRT).

4. Study endpoints and statistical analysis
The primary endpoint was to define predictive factors for changes of NLR, neutrophil counts, and lymphocyte counts between before and after radiation. Secondary endpoints were changes of NLR, neutrophil counts, and lymphocyte counts between the 3D-CRT group and the IMRT group.

Factors associated with changes of ANC, ALC, or NLR were identified using simple and multiple linear regression. The forward and backward stepwise methods were used to select predictive variables in a multiple linear regression. The normality, independence, linearity, and homoscedasticity were checked for suitability of linear regression. Factors affecting severe lymphopenia were determined by logistic regression. Means of the 3D-CRT group and the IMRT group were compared using Shapiro-Wilk test, Fisher F test, and t-test. All statistical analyses were performed using R version 4.2.1 (https://cran.r-project.org/). Results were assessed as statistically significant when p-values were less than 0.05.

Results

1. Change of white blood cell counts
A total of 41 patients were evaluated. At baseline, the median neutrophil count was 3,280/µL (range, 1,720 to 7,860/µL) and the median lymphocyte count was 1,950/µL (range, 940 to 3,710/µL). Median baseline value of NLR was 1.67 (range, 0.48 to 3.63) (Table 1). The median size of PTV was 75.5 mL (range, 3.7 to 649.2 mL) and the mean dose to whole brain was 1,219 cGy (range, 480 to 3,907 cGy) (Table 1). Overall, white blood cell (WBC) count decreased only in 20 patients (48.8%). The median difference of WBC changes between before and after radiotherapy was minimal (+20/µL). Although the ANC was increased in 25 patients (61.0%) by a median of 42/µL, ALC was decreased in 32 patients (78.1%) with a median of -338/µL. Therefore, NLR was increased in 31 patients (75.6%) by a median of 41.2%. At the end of the RT, no patient developed grade 2 or higher neutropenia, neutrophilia, or lymphopenia by the median of -338/µL. Therefore, NLR was increased in 31 patients (75.6%) by a median of 41.2%. At the end of the RT, no patient developed grade 2 or higher neutropenia, neutrophilia, or lymphopenia. The median size of PTV was 75.5 mL (range, 3.7 to 649.2 mL) and the mean dose of brain were increased, there were trends toward a decrease in lymphocyte count (p = 0.078 and p = 0.073, respectively). Other clinical and dosimetric factors were not related to changes of ANC (Table 3). In a multivariate analysis, only brain V15 remained statistically significant.

Severe lymphopenia defined as a decrease of ALC by 500/µL or more was observed in 13 patients (31.7%). Mean brain V15 (25.7% vs. 21.1%, p = 0.037), V10 (59.0% vs. 38.3%, p = 0.022), and V15 (47.5% vs. 29.6%, p = 0.012) were significantly higher in these patients than in others. In logistic regression analysis, V10 was the most significant factor with a hazard ratio (HR) of 1.041 (95% confidence interval [CI], 1.007–1.076, p = 0.016) (Table 4).

3. Factors affecting absolute neutrophil count (ANC)
In both linear and logistic regression analyses, it was difficult to find predictive factors affecting the change of ANC (Tables 3, 5). The mean brain V15 was higher in patients with neutrophilia (increase of ANC) than in patients with neutropenia (13.8% vs. 7.5%) with a marginal significance (p = 0.067) in a t-test. However, it was not significant in regression analysis.

4. Factors affecting NLR
There was a correlation between lymphopenia (decrease of ALC) and 

| Table 2. Clinical treatment characteristics of patients (n = 41) |
|------------------|------------------|
| Characteristic   | Value            |
| Delivered total dose (cGy) | 4,140 (2,000–5,580) |
| Fraction size (cGy)            | 180 (180–240)     |
| RT duration (day)              | 42 (28–55)        |
| PTV size (mL)                  | 75.5 (3.7–649.2)  |
| Brain Dmax (cGy)               | 5,302 (4,685–6,443) |
| Brain D15 (cGy)                | 37 (0–146)        |
| Brain D15 (cGy)                | 1,219.5 (480–3,907) |
| Brain V10 (%)                  | 48.2 (15.1–97.4)  |
| Brain V15 (%)                  | 41.3 (11.7–94.1)  |
| Brain V10 (%)                  | 30.6 (9.7–89.6)   |
| Brain V15 (%)                  | 24.15 (8.5–82.9)  |
| Brain V10 (%)                  | 19.5 (5.9–77.7)   |
| Brain V15 (%)                  | 17.05 (4.3–601)   |
| Brain V10 (%)                  | 12.9 (3.2–67.4)   |
| Brain V15 (%)                  | 10.5 (2.4–62.5)   |
| Brain V10 (%)                  | 8.6 (1.7–56.6)    |

Values are presented as median (range). RT, radiation therapy; PTV, planning target volume.

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Fig. 1. (Left) Liner regression of absolute lymphocyte count (ALC) change with brain V15. If we expanded 1% of brain V15, we could expect lymphocyte counts to decrease by approximately 7.95/µL. (Right) The normality, independence, linearity, and homoscedasticity were checked for suitability of linear regression.

### Table 3. Linear regression analysis for changes of ANC, ALC, and NLR

<table>
<thead>
<tr>
<th></th>
<th>ANC (Coefficient (B))</th>
<th>p-value</th>
<th>ALC (Coefficient (B))</th>
<th>p-value</th>
<th>NLR (Coefficient (B))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.703</td>
<td>0.639</td>
<td>-121.55</td>
<td>0.499</td>
<td>0.626</td>
<td>0.432</td>
</tr>
<tr>
<td>PTV (mL)</td>
<td>0.306</td>
<td>0.865</td>
<td>-1.18</td>
<td>0.078</td>
<td>0.078</td>
<td>0.443</td>
</tr>
<tr>
<td>Brain mean dose (cGy)</td>
<td>-0.073</td>
<td>0.793</td>
<td>-0.18</td>
<td>0.073</td>
<td>0.006</td>
<td>0.717</td>
</tr>
<tr>
<td>Brain V5 (%)</td>
<td>-7.820</td>
<td>0.403</td>
<td>-5.06</td>
<td>0.152</td>
<td>-0.175</td>
<td>0.741</td>
</tr>
<tr>
<td>Brain V5 (%)</td>
<td>-5.472</td>
<td>0.570</td>
<td>-6.93</td>
<td>0.050</td>
<td>0.079</td>
<td>0.885</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>-3.943</td>
<td>0.711</td>
<td>-7.95</td>
<td>0.043^a</td>
<td>0.282</td>
<td>0.639</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>-3.752</td>
<td>0.753</td>
<td>-8.31</td>
<td>0.059</td>
<td>0.340</td>
<td>0.613</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>-2.591</td>
<td>0.845</td>
<td>-8.47</td>
<td>0.085</td>
<td>0.417</td>
<td>0.576</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>2.608</td>
<td>0.857</td>
<td>-7.59</td>
<td>0.160</td>
<td>0.406</td>
<td>0.618</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>5.041</td>
<td>0.754</td>
<td>-7.68</td>
<td>0.201</td>
<td>0.489</td>
<td>0.589</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>5.507</td>
<td>0.751</td>
<td>-8.69</td>
<td>0.181</td>
<td>0.565</td>
<td>0.563</td>
</tr>
<tr>
<td>Brain V10 (%)</td>
<td>8.018</td>
<td>0.673</td>
<td>-9.42</td>
<td>0.185</td>
<td>0.682</td>
<td>0.524</td>
</tr>
<tr>
<td>RT duration</td>
<td>-24.730</td>
<td>0.575</td>
<td>-19.34</td>
<td>0.238</td>
<td>-0.531</td>
<td>0.830</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil counts; ALC, absolute lymphocyte counts; NLR, neutrophil-to-lymphocyte ratio; PTV, planning target volume; RT, radiation therapy.

^aStatistically significant in simple linear regression and ^bstatistically significant in simple and multiple linear regression.

and increase of NLR with Pearson correlation coefficient of 0.641 (p < 0.001) (Fig. 2). However, in both linear and logistic regression analyses, there was no significant factor that could predict NLR changes (Tables 3, 5).

### 5. Comparison between 3D-CRT and IMRT

We also compared cell count differences between 3D-CRT and IMRT groups. Mean differences of ALC, ANC, and NLR were no statistically significant between 3D-CRT and IMRT groups (Fig. 3). Although the radiation dose to the brain was slightly higher for the low-dose area in the IMRT group and higher for the higher dose area in the 3D-CRT group, these differences were not statistically different (Fig. 4). The PTV volume and brain mean dose were also similar between 3D-CRT and IMRT groups.

### Discussion and Conclusion

The relationship between NLR and high-grade glioma (HGG) has been evaluated in several prior studies [2,3]. Most of such studies were focused on the association of pre-treatment NLR and prog-
**Table 4.** Logistic regression analysis for severe ALC decline (more than 500/μL)

<table>
<thead>
<tr>
<th></th>
<th>Coefficient (B)</th>
<th>Exp(B) (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 60 vs. &gt; 60 yr)</td>
<td>-0.629</td>
<td>0.533 (0.131–2.178)</td>
<td>0.381</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>-0.613</td>
<td>0.542 (0.142–2.072)</td>
<td>0.370</td>
</tr>
<tr>
<td>RT technique (3D-CRT vs. IMRT)</td>
<td>0.954</td>
<td>2.596 (0.654–10.448)</td>
<td>0.179</td>
</tr>
<tr>
<td>PTV (mL)</td>
<td>0.005</td>
<td>1.005 (0.999–1.011)</td>
<td>0.128</td>
</tr>
<tr>
<td>Brain mean dose (cGy)</td>
<td>0.001</td>
<td>1.001 (1.000–1.002)</td>
<td>0.033&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>0.036</td>
<td>1.036 (1.004–1.070)</td>
<td>0.027&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;2&lt;/sub&gt; (%)</td>
<td>0.040</td>
<td>1.041 (1.007–1.076)</td>
<td>0.016&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;3&lt;/sub&gt; (%)</td>
<td>0.042</td>
<td>1.043 (1.006–1.081)</td>
<td>0.024&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;4&lt;/sub&gt; (%)</td>
<td>0.040</td>
<td>1.041 (1.001–1.082)</td>
<td>0.046&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;5&lt;/sub&gt; (%)</td>
<td>0.040</td>
<td>1.041 (0.998–1.086)</td>
<td>0.064</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;6&lt;/sub&gt; (%)</td>
<td>0.039</td>
<td>1.040 (0.994–1.088)</td>
<td>0.091</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;7&lt;/sub&gt; (%)</td>
<td>0.039</td>
<td>1.040 (0.990–1.093)</td>
<td>0.121</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;8&lt;/sub&gt; (%)</td>
<td>0.044</td>
<td>1.045 (0.990–1.103)</td>
<td>0.113</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;9&lt;/sub&gt; (%)</td>
<td>0.049</td>
<td>1.050 (0.989–1.115)</td>
<td>0.112</td>
</tr>
<tr>
<td>RT duration (days)</td>
<td>0.073</td>
<td>1.076 (0.001–1.239)</td>
<td>0.311</td>
</tr>
</tbody>
</table>

ALC, absolute lymphocyte counts; RT, radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; CI, confidence interval.  
<sup>a</sup>Statistically significant in simple linear regression and <sup>b</sup>statistically significant in simple and multiple linear regression.

**Table 5.** Logistic regression for neutrophilia, lymphopenia, and increasement of NLR

<table>
<thead>
<tr>
<th></th>
<th>Neutrophilia (ANC increase)</th>
<th>Lymphopenia (ALC decrease)</th>
<th>NLR increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (B)</td>
<td>Exp(B) (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age (&lt; 60 vs. &gt; 60 yr)</td>
<td>0.891 (0.545–10.898)</td>
<td>2.437 (0.986–10.590)</td>
<td>0.395</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>-0.752 (0.131–1.702)</td>
<td>0.471 (0.251–0.840)</td>
<td>0.525</td>
</tr>
<tr>
<td>RT technique (3D-CRT vs. IMRT)</td>
<td>0.241</td>
<td>1.273 (0.362–4.480)</td>
<td>0.492</td>
</tr>
<tr>
<td>PTV (mL)</td>
<td>0.007 (0.998–1.015)</td>
<td>1.007 (0.996–1.023)</td>
<td>0.361</td>
</tr>
<tr>
<td>Brain mean dose (cGy)</td>
<td>0.001 (1.000–1.001)</td>
<td>1.001 (1.000–1.002)</td>
<td>1.000</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>0.002 (0.976–1.029)</td>
<td>1.002 (0.991–1.070)</td>
<td>0.649</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;2&lt;/sub&gt; (%)</td>
<td>0.008 (0.980–1.037)</td>
<td>1.008 (0.995–1.092)</td>
<td>0.797</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;3&lt;/sub&gt; (%)</td>
<td>0.017 (0.984–1.051)</td>
<td>1.017 (0.987–1.095)</td>
<td>0.629</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;4&lt;/sub&gt; (%)</td>
<td>0.023 (0.984–1.064)</td>
<td>1.024 (0.979–1.094)</td>
<td>0.566</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;5&lt;/sub&gt; (%)</td>
<td>0.029 (0.984–1.076)</td>
<td>1.029 (0.973–1.092)</td>
<td>0.649</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;6&lt;/sub&gt; (%)</td>
<td>0.040 (0.986–1.099)</td>
<td>1.041 (0.964–1.083)</td>
<td>0.496</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;7&lt;/sub&gt; (%)</td>
<td>0.049 (0.986–1.119)</td>
<td>1.050 (0.958–1.088)</td>
<td>0.523</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;8&lt;/sub&gt; (%)</td>
<td>0.050 (0.982–1.125)</td>
<td>1.051 (0.955–1.100)</td>
<td>0.568</td>
</tr>
<tr>
<td>Brain V&lt;sub&gt;9&lt;/sub&gt; (%)</td>
<td>0.063 (0.981–1.156)</td>
<td>1.065 (0.946–1.094)</td>
<td>0.504</td>
</tr>
<tr>
<td>RT duration (days)</td>
<td>-0.043 (0.841–1.091)</td>
<td>0.958 (0.693–0.999)</td>
<td>0.864</td>
</tr>
</tbody>
</table>

NLR, neutrophil-to-lymphocyte ratio; ANC, absolute neutrophil counts; ALC, absolute lymphocyte counts; RT, radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume.  
<sup>p</sup> < 0.05.
nosis. Gan et al. [3] have reported that pretreatment high NLR (cutoff value 3) is an unfavorable predictor of prognosis for elderly patients with HGG. Mason et al. [2] have investigated dynamic changes of NLR during chemoradiation and demonstrated that those with a decline of NLR during treatment have better survival than those without a decline in NLR. Interestingly, although the dynamic change of NLR remained significant with OS (p = 0.0031), the pre-treatment NLR was no longer statistically relevant (p = 0.9127). Ahn et al. [8] have shown that glioblastoma patients with total lymphocyte count (TLC) < 1,200 cells/mm³ at 4 weeks after completion of concurrent chemoradiotherapy show shorter survival than those with TLC ≥ 1,200 cells/mm³ (median OS, 14.5 vs. 21.0 months; p = 0.017). Therefore, we focused on dynamic changes of NLR before and after radiation and factors lowering NLR values, which might produce a better prognosis.

With respect to low-grade glioma, preoperative NLR has also been found to be an independent prognostic parameter of PFS and OS. Tan et al. [9] evaluated 119 patients with WHO II gliomas and

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**Fig. 2.** Correlation the change between absolute lymphopenia count (ALC) and neutrophil-to-lymphocyte ratio (NLR).

**Fig. 3.** Mean differences of (A) lymphocyte, (B) neutrophil and (C) NLR change between RT techniques (3D-CRT vs. IMRT). NLR, neutrophil-to-lymphocyte ratio; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiation therapy.
concluded that preoperative high NLR with a cut-off value of 1.875 was significantly correlated with greater relapse and poor prognosis.

The correlation between survival and lymphopenia has also been shown in prior studies on solid tumors [7]. Kang et al. [10] analyzed 272 non-small cell lung cancer (NSCLC) patients treated by definite chemoradiation. Delayed lymphopenia was associated with inferior survival and lung $V_{5}$ was the most important predictive dosimetric factor. Furthermore, grade ≥ 3 lymphopenia might be associated with a higher hazard for hospital admission with an infection [6]. Treatment-related lymphopenia could lead to an increased risk for death in cancer cohorts including malignant glioma (HR = 1.8; 95% CI, 1.13–2.87) [7]. Therefore, trying to reduce the risk of lymphopenia is reasonable.

In our study, ALC was decreased in 32 patients (78.1%) while NLR was increased in 31 patients (75.6%). Increasing low dose to the brain (such as $V_{5}$, $V_{10}$, and $V_{15}$) might be associated with lymphopenia, which might give rise to elevated NLR. However, in brain tumor patients treated with radiation alone, the effect of radiation on lymphopenia was minimal. Only one patient experienced grade 1 lymphopenia after radiotherapy, while there was no grade 2 or higher hematologic toxicities. In addition, it was difficult to find dosimetric factors affecting the change of ANC. Therefore, it seems that the increase of NLR is not definitely correlated with radiation alone.

In addition, it has been found that tumor-associated neutrophilia is associated with poor clinical outcome in several solid cancers [11-13]. Pretreatment neutrophilia is also relevant to worse OS in malignant glioma [14]. Glucocorticoids can prolong neutrophil survival in vitro by inhibiting its apoptosis and result in neutrophilia [15,16]. Although the correlation between mean baseline dexamethasone dose and NLR was weak in a previous study [2], there is a possibility of connection between glucocorticoids and immune cells. In this sense, our analysis tried to exclude patients who had received high doses of steroids.

The volume of brain receiving radiation can be a significant dosimetric predictor of post-treatment lymphopenia. Previous studies have demonstrated that brain $V_{25}$ is a sole predictive dosimetric factor for severe post-treatment lymphopenia in HGG [17]. Maintaining $V_{25Gy}$ of the brain below 56% might reduce the risk of acute severe lymphopenia [17]. In addition, it has been revealed that lymphocyte nadirs are significantly correlated with lower doses in lung $V_{5}$–$V_{10}$ (p < 0.0001) of NSCLC patients [18]. In the present study, we found that the volume of brain exposed to a low dose of radiation during RT was associated with the development of lymphopenia, with brain $V_{5}$, $V_{10}$, and $V_{15}$ as significant dosimetric parameters. Therefore, efforts to reduce these low doses should be made to prevent lymphopenia in patients treated the brain by RT alone. Particle therapy, avoiding routine use of multiple beams or arc therapy can be an option to reduce low doses to normal brain.

However, in terms of radiotherapy technique there are also conflicting results. In one study of glioblastoma, the incidence of acute severe lymphopenia was lower in the IMRT group than in the 3D-CRT group [19]. In our study, we could not demonstrate a significant difference between 3D-CRT and IMRT groups in low-grade brain tumors. This might be due to small differences of brain doses between 3D-CRT and IMRT groups. It might also be due to the fact that the majority of patients (12 out of 19) in the 3D-CRT group

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**Fig. 4.** Comparison of dose-volume histogram between radiation techniques RT techniques (3D-CRT vs. IMRT). 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RT, radiation therapy.
were treated with non-coplanar beams. These beam alignments might have reduced the difference in low brain dose between 3D-CRT and IMRT groups.

This study has several limitations. First, this was a retrospective study performed in a single institution with a small sample size. Several patients who received a high dose of steroid due to brain edema were excluded from analysis, leading to a small sample size. Another limitation was that the timing of blood sampling was different. In addition, it was difficult to determine the persistence of lymphopenia because post-treatment follow-up laboratory data was missing in more than half of the patients.

In conclusion, a decrease of ALC and an increase of NLR were observed in three-fourth of patients in low-grade brain tumor patients treated by RT alone. The decrease of ALC was mainly affected by low dose to the brain such as $V_{10}$, $V_{15}$, and $V_{20}$. However, we could not find a correlation between RT dose and changes of ANC or NLR. Further evaluations with a larger group of patients and a regular timing of blood collection are needed to draw a definite conclusion.

Statement of Ethics

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (No. KC22RISI0266).

Conflict of Interest

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

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Author Contributions

Conceptualization, Song JH. Investigation and methodology, Choi YK, Jang HS. Supervision, Song JH, Choi BO. Writing of the original draft, Choi YK, Lee SW. Writing of the review and editing, Choi YK, Song JH. Formal analysis, Choi YK, Lee SW. Data curation, Jang HS, Choi BO. Visualization, Choi YK, Song JH.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Radiotherapy combined with immunotherapy could improve the immune infiltration of melanoma in mice and enhance the abscopal effect

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Purpose: To analyze the gene mutation, immune infiltration and tumor growth of primary tumor and distant tumor under different treatment modes.

Materials and Methods: Twenty B16 murine melanoma cells were injected subcutaneously into the of both sides of the thigh, simulating a primary tumor and a secondary tumor impacted by the abscopal effect, respectively. They were divided into blank control group, immunotherapy group, radiotherapy group, and radiotherapy combined immunotherapy group. During this period, tumor volume was measured, and RNA sequencing was performed on tumor samples after the test. R software was used to analyze differentially expressed genes, functional enrichment, and immune infiltration.

Results: We found that any treatment mode could cause changes in differentially expressed genes, especially the combination treatment. The different therapeutic effects might be caused by gene expression. In addition, the proportions of infiltrating immune cells in the irradiated and abscopal tumors were different. In the combination treatment group, T-cell infiltration in the irradiated site was the most obvious. In the immunotherapy group, CD8+ T-cell infiltration in the abscopal tumor site was obvious, but immunotherapy alone might have a poor prognosis. Whether the irradiated or abscopal tumor was evaluated, radiotherapy combined with anti-programmed cell death protein 1 (anti-PD-1) therapy produced the most obvious tumor control and might have a positive impact on prognosis.

Conclusion: Combination therapy not only improves the immune microenvironment but may also have a positive impact on prognosis.

Keywords: Melanoma, Abscopal effect, Radiotherapy, Anti-PD-1 antibody, Immune response, RNA sequence analysis

Introduction

Melanoma is a skin cancer caused by malignant melanocytes and is highly malignant [1]. In recent years, its incidence rate has increased sharply, and this increase in rate is faster than that of other types of cancer, which has become a thorny public health problem [2,3]. Several subtypes of melanoma have been defined, including uveal, mucosal, meningeal, anorectal and the most common type,
cutaneous. The differences in prognosis among these subtypes mainly depend on the stage at diagnosis [3,4]. Early diagnosis is crucial for improving prognosis because most of the complications of melanoma come from metastasis and its impact on the affected organs [5].

To treat local or metastatic tumors, the primary melanoma and metastatic tumors should be surgically removed as completely as possible for therapeutic purposes [6]. In addition, melanoma is an immunogenic tumor [7], and the efficacy of immune checkpoint inhibitors has been shown to be superior to that of conventional drugs. At present, nivolumab monotherapy, pembrolizumab monotherapy, and nivolumab combined with ipilimumab are the first choices for systemic immunotherapy for patients with advanced melanoma [8-10]. However, less than 50% of patients show a persistent antitumor response and benefit from immunotherapy alone, and a considerable proportion of patients show drug resistance [11,12].

Radiotherapy is usually considered a local treatment for cancer. However, in recent years, an increasing number of studies have shown that radiotherapy can induce tumor regression outside the irradiation field in solid cancers. This systemic response is called the abscopal effect [13]. The occurrence of the abscopal effect is related to the specific immune activation caused by radiation-induced cell death [14]. Before the advent of immunotherapy, a review of the abscopal effect of radiotherapy showed that only 46 cases of the abscopal effect were reported among the millions of patients receiving treatment [15]. Immune checkpoint inhibitors can enhance the function of T cells, so an increasing number of studies have evaluated the effect of combining immunotherapy and radiotherapy on primary and abscopal tumors. During immunotherapy, the observation of an abscopal response in patients receiving palliative radiotherapy due to tumor progression is helpful for understanding the immunogenicity of radiotherapy and the potential mechanism of its interaction with cancer immunotherapy [16,17]. The results have shown that the addition of immunotherapy significantly enhances the abscopal effect-induced impact of radiotherapy and that radiotherapy may increase the immunogenicity of tumors and reprogram them [14,18].

The purpose of our study is to analyze the gene expression in primary tumor and abscopal tumor from a genetic perspective and the effect of different treatment methods on immune infiltration and prognosis by establishing a mouse abscopal tumor model with the help of R language (https://www.r-project.org/).

Materials and Methods

1. Mice
Twenty C57BL/6 mice (6 to 10 weeks of age) with the same mouse source were obtained from Cavens Laboratory Animal Co., Ltd. Mice were treated according to a protocol approved by the Animal Care and Use Committee of Soochow University (No. SUDA2022102A02). While housed on a 12-hour light/dark cycle, mice were given free access to food and water.

2. Animal model construction
After 7 days of feeding, 5 × 10^5 B16 cells in 1,250 μL phosphate-buffered saline (PBS) were subcutaneously injected into the right thigh of mice to simulate a primary tumor (irradiated tumor), and 3 × 10^5 B16 cells in 750 μL PBS were injected under the skin of the left thigh to simulate a secondary tumor (abscopal tumor), this timepoint was considered day 0. The B16-F10 mouse melanoma cell line were purchased from BeNa Culture Collection (Suzhou, China).

When the tumor volume reached 150 mm³, the mice were randomly divided into four groups: control group, immunotherapy group, radiotherapy group, and radiotherapy combined with immunotherapy group. The immunotherapy scheme was to intraperitoneally inject anti-mouse programmed cell death protein 1 (PD-1) (10 mg/kg) five times [19], specifically on the 10th, 12th, 14th, 16th, and 18th days of the experiment. Purified anti-mouse PD-1 was purchased from Shanghai Junshi Biological Science Co., Ltd. For the radiotherapy group, on the 14th day, the right thigh of each mouse was irradiated with a single dose of 20 Gy of 6 MeV electron rays from the Elekta Infinity linear accelerator. The irradiation field was 20 cm × 5 cm and the SSD was 100 cm. Irradiate five mice side by side each time. The control group did not receive any treatment.

3. Tumor growth measurement
Tumor volume was measured every 2 days by an electronic caliper, and the following formula was used to calculate the volume:

\[
Volume = \frac{\pi}{6} \times ab^2,
\]
where a and b in the formula are the long and short axes of the two orthogonal diameters, respectively.

4. Survival rate assessment
Mice were monitored daily to assess their survival over a 20-day period. Survival time was recorded as the time until the date of death. Mice were euthanized by carbon dioxide gas asphyxiation when the experiment was over or when they exhibited signs of poor body condition following the Institutional Animal Care policy and guidelines approved by the American Veterinary Medical Association.
5. RNA sequencing

At the end of the experiment, one mouse in each group was selected for RNA sequencing of its primary tumor and secondary tumor (all mice come from the same mouse source, and each group of mice receives the same treatment mode). All sequencing was conducted on an Illumina HiSeq Platform (Illumina Inc., San Diego, CA, USA) with 200-bp paired-end reads following the manufacturer’s protocol. Initial quality control of the RNA sequencing data was performed with the FastQC tool. For each sample, STAR aligner was used to align the short reads to the GRCh38/mm10 reference genome. For the expression of mRNA transcripts, normalized fragments per kilobase per million mapped reads (FPKM) were obtained using the robust FPKM estimate function of the DESeq2 tool.

6. Bioinformatic analysis

For human analyses, the mouse gene IDs were converted to human gene IDs via R package “biomaRt.” For mRNA transcripts, DESeq software was used to screen known transcripts differentially expressed between different sample groups; differentially expressed genes met the threshold of $|\log_{2}FC| \geq 1$ and $p \leq 0.05$. A volcano plot and heatmap were used to visualize the different genes in different samples.

For analyzing the immune cell types in all of the sample genes, CIBERSORT (http://cibersort.stanford.edu/) was used to calculate the composition of immune cells from gene expression profiles. All gene expression matrix from eight samples were imported in CIBERSORT website, CIBERSORT’s LM22 signature matrix was used as the reference to estimate the proportions of nine kinds of immune cells in the RNA-seq samples. R package “ESTIMATE” was used to predict tumor purity.

The Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed using the clusterProfiler package in R. The GO terms and KEGG pathways were considered statistically significant if their p-values and false discovery rates (FDR) were less than 0.05.

7. Statistical analysis

R software (version 4.1.0) was used to process data, and R language was used for visualization. GraphPad 8.0 software was also used for visualization, and data are presented as the mean ± standard error or mean ± standard deviation as indicated. The difference between two groups of samples passed the Wilcoxon test. $p < 0.05$ was considered statistically significant.

Results

1. Difference in gene expression profiles between irradiated tumors and abscopal tumors

To fully reflect the advantages of radiotherapy combined with anti-PD-1 immunotherapy versus the other three treatment modes, one mouse was selected from each of the four groups on the 20th day of the experiment, and the primary tumor and secondary tumor were isolated. A total of eight samples were sent for RNA sequencing. Volcano plot results showed that compared with the control group, the combination treatment group contained 641 differentially expressed genes, including 92 genes that were upregulated and 549 genes that were downregulated (Fig. 1A). There were 170 differentially expressed genes between the immunotherapy only group and the combination treatment group, including 50 genes that were upregulated and 120 genes that were downregulated (Fig. 1B). Compared with the radiotherapy alone group, the combination treatment group contained 33 genes that were upregulated and 86 genes that were downregulated, with a total of 119 differentially expressed genes (Fig. 1C). In addition, we found that both irradiated tumors and abscopal tumors could have differential gene changes, but these were mainly found in the irradiated tumors (Fig. 1D–1F). In short, whether irradiated or abscopal tumors are assessed, there will be changes in differential genes.

2. Radiotherapy combined with anti-PD-1 therapy changed the enriched pathways of differential genes between irradiated and abscopal tumors

Next, we further compared the pathways related to differential gene enrichment between radiotherapy combined with anti-PD-1 therapy and the other three groups. We first conducted GO enrichment analysis, and the results showed that in the radiotherapy combined with anti-PD-1 treatment group and the blank control group, the differentially expressed genes had significant changes in biological processes, cellular components, and molecular functions (Fig. 2A). In the comparisons of the radiotherapy combined with anti-PD-1 therapy group with the immunotherapy only group or radiotherapy only group, the changes in the differential gene-related enriched pathways were mainly reflected in biological processes and biological functions (Fig. 2B, 2C). Then, KEGG enrichment analysis results showed that in the comparison between radiotherapy combined with anti-PD-1 therapy and immunotherapy alone, the results were not statistically significant (adjusted $p > 0.05$) (Fig. 2D), while in the other comparisons, eight overlapping pathways, such as tuberculosis and toxoplasmosis, were identified, but the pathways related to a local inflammatory reaction, such as the chemokine signaling pathway and cell adhesion molecules, were
Fig. 1. Genes change differently under different treatment modes. (A–C) The volcanic maps show the differences in gene expression between the combination therapy group and the control group, immunotherapy group, and radiation therapy group, respectively. (D–F) The thermograms show the differential genes between irradiated tumor and abscopal tumor “A” represents blank control group, “B” represents simple immunotherapy group, “C” represents radiotherapy group, “D” represents radiotherapy combined immunotherapy group, “1” represents primary tumor, and “2” represents secondary tumor (the same below). p < 0.05 was statistically significant.

significantly changed. The above results showed that different treatment modes, especially radiotherapy combined with immunotherapy, could cause changes in the enrichment of differentially expressed genes, which was mainly reflected the local inflammatory response-related pathways connected to antitumor activity.

3. Radiotherapy combined with anti–PD–1 therapy improved the immune microenvironment
The anti-tumor immune response depends on the proportion and function of cells in the tumor microenvironment. With the help of R language, we determined the percentages of 22 kinds of infiltrat-
The KEGG enrichment analysis (A vs. D)

Combined treatment improves prognosis

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Fig. 2. Analysis of differential genes enrichment pathways. (A–C) The Gene Ontology (GO) enrichment analysis of differential genes between the combined treatment group and other groups. Red represents biological process (BP), green represents cellular component (CC), and blue represents molecular function (MF). (D–F) The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis of differential genes between the combined treatment group and other groups. Adjusted p < 0.05 is statistically significant. “A” and “D” are differential genes between the combination therapy group and the control group; “B” and “E” are differential genes between the combination therapy group and the immunotherapy group; “C” and “F” are differential genes between the combination therapy group and the radiation therapy group.
Fig. 3. The proportion of immune cells in primary and abscopal tumors is different under different treatment modes. (A) Twenty-two kinds of immune cells infiltrate in different groups, and different colors represent different immune cells. (B, C) Pie chart shows that the proportion of main immune cells in each sample changes due to different treatment modes. (D, E) The purity of primary tumor and secondary tumor changes under different treatment modes. mDC, mature dendritic cell.
Infiltration level between samples

![Infiltration level between samples](image)

**Fig. 4.** The proportion of main immune cells in different parts of the same mouse is different. mDC, mature dendritic cell.

The proportion of main immune cells in different parts of the same mouse is different. mDC, mature dendritic cell.

ing immune cells in each sample (Fig. 3A). The degree of infiltration of each sample cell was different, but in general, the immune infiltrate was dominated by resting dendritic cells and monocytes. The T cell surface receptor PD-1 plays a key role in inhibiting the T cell response. Next, we drew a pie chart to further illustrate the differences in the percentages of immune cells in different treatment modes (Fig. 3B, 3C). In irradiated tumors, the infiltration of CD8+ T cells in both the radiotherapy group and the anti-PD-1 treatment group was increased compared with that in the blank group. In the radiotherapy combined with immunotherapy group, the infiltration of T cells was further increased. Thus, radiotherapy combined with immunotherapy was considered to improve the local infiltration of T cells. In addition, compared with other groups, the combination treatment group showed a significant change in the degree of infiltration of macrophages, monocytes, and mature dendritic cells (mDCs). In abscopal tumors, the proportions of immune cells in the control group and the immunotherapy alone group were not significantly different. Radiotherapy could increase the infiltration of monocytes in the abscopal site. The combination therapy group showed significant infiltration of mDC and T cell CD4+ compared to the radiotherapy group alone. The proportion of CD8+ T cells in the abscopal tumor in the combination treatment group was higher than that in the blank control group, but it was not significantly higher than that in the irradiated tumor. Finally, we compared the tumor purity of different sites, and the results showed that radiotherapy combined with anti-PD-1 treatment could significantly reduce the tumor purity of primary tumors, while in abscopal tumors, the tumor purity of the immunotherapy group was significantly decreased (Fig. 3D, 3E). It could be seen that different treatment modes had varying therapeutic effects on primary and distant tumors. For primary lesions, radiotherapy combined with immunotherapy was more effective, while for abscopal tumors, immunotherapy alone was more effective than combination therapy. The addition of immunotherapy on the basis of radiotherapy can significantly improve the immune microenvironment, which may be beneficial in guiding clinical treatment.

4. The abundance of immune cells in abscopal and irradiated sites was significantly changed in the radiotherapy combined with anti-PD-1 treatment group

Then, we compared the difference in the tumor immune microenvironment between the irradiated site and abscopal site. The results showed that different treatment modes caused different immune cell abundances in irradiated tumors and abscopal tumors (Fig. 4).

Among the treatment modes, the radiotherapy combined with anti-PD-1 treatment group showed the greatest impact, the immunotherapy group showed the smallest impact, and the radiotherapy group was between the two. In the radiotherapy combined with anti-PD-1 treatment group, the difference in immune cell infiltration between irradiated tumors and abscopal tumors was mainly reflected in CD8+ T cells, CD4+ T cells, macrophages, monocytes, and mDCs, and the abundances of the above immune cells at the irradiated site were greater than those at the abscopal site, showing good local control.

5. Radiotherapy combined with anti-PD-1 therapy enhanced the control of irradiated tumors and abscopal tumors

To study the control of local and abscopal tumors achieved with radiotherapy combined with immunotherapy, we measured the tumor volume in the mouse abscopal effect model we established every 2 days after the tumor volume reached 150 mm$^3$ (Supplementary Figs. S1, S2). The results showed that for the primary tumor, the tumor volume of the combination treatment group was significantly smaller than that of the control group ($p<0.01$) (Fig. 5A), followed by the radiotherapy group, and immunotherapy had the weakest ability to reduce tumor volume. Among the secondary tumors, radiotherapy alone had the weakest reducing effect on tumor volume, while radiotherapy combined with immunotherapy had a significantly better tumor volume-reducing effect than the other treatments (Fig. 5B). Finally, on the 20th day of the experiment, tumors were isolated from mice (Fig. 5C). The effect of immunotherapy on the volume of secondary tumors was more obvi-
A more than that of radiotherapy alone or control treatment. The number of tumor cells subcutaneously injected to produce the secondary tumors was less than that used to establish the primary tumors, reflecting the difference in the immunosuppressive ability of immunotherapy against tumors of different volumes. Whether it was primary tumor or secondary tumors, the tumor volume in the combination therapy group was significantly reduced compared to other groups, but the change in mouse weight was not very significant (Supplementary Table S1). The mice in the immunotherapy group died on the 14th day of the experiment, the mice in the radiotherapy group died on the 16th day of the experiment, and the mice in the combination treatment group with the most obvious tumor volume reduction all lived to the end of the experiment. In summary, receiving immunotherapy alone may cause immunotoxicity and a poor prognosis. Whether considering irradiated tumors or abscopal tumors, radiotherapy combined with anti-PD-1 had the most obvious effect achieving tumor control and might have a positive impact on prognosis (Fig. 5D).

Discussion and Conclusion

At present, there are various immune checkpoint blocking therapies for basic and clinical research, among which inhibitors targeting immune checkpoint cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and PD-1 molecules are at the forefront of immunotherapy [20-22]. Changes in tumor microenvironment will affect the therapeutic effect of PD-1/PD-L1 (programmed death-ligand 1) monoclonal antibody [23,24]. More and more studies have shown that radiation therapy combined with PD-1/PD-L1 monoclonal antibody can effectively expand the population benefiting from immunotherapy. There are two main mechanisms by which radiotherapy induces anti-tumor immune responses: firstly, radiotherapy kills tumor cells through radiation, significantly reducing tumor burden and alleviating tumor mediated immunosuppression [25]. The second is that radiotherapy induces immunogenic death of tumor cells and activates adaptive immunity. Radiation therapy can not only enhance local anti-tumor responses, but also produce ab-

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Fig. 5. Establish a model of radiotherapy-abscopal effect in mice. (A, B) Tumor growth curve of irradiated and non-irradiated parts. N represents control group, ICB represents simple immunotherapy, RT represents simple radiotherapy. (C) Primary and secondary tumors isolated from mice were compared. From top to bottom are the control group, immunotherapy group, radiation therapy group, and combination therapy group. The missing part is the death of mice. (D) Survival percentage of each group of mice (number of surviving mice/7 * 100%). Experimental groups contained at least seven mice and are representative of two independent experiments. N: normal group; ICB: immune checkpoint blockade; RT: radiotherapy group; RT+ICB: combined therapy of RT and ICB.
Malignant melanoma is a highly invasive tumor, and approximately 15% of patients have metastasis at the time of diagnosis [26]. Radiotherapy plays an important role in the treatment of metastatic melanoma [27]. Radiotherapy can cause differential gene expression changes, which has been widely confirmed in a variety of tumors. In our study, we found that immunotherapy could cause differential gene expression. In the radiotherapy combined with immunotherapy group, the number of differentially expressed genes was the largest, but it was not the sum of the number of differentially expressed genes resulting from radiotherapy or immunotherapy alone. According to current research, radiotherapy can activate the antitumor immune response [28], and immunotherapy has been proven to have a synergistic effect with radiation-induced immune activation [29,30]. We speculated that the interaction between radiotherapy and immunotherapy may be fundamentally caused by different genes, which further affects the changes in the antitumor pathway seen with different treatment schemes, directly leading to different antitumor effects.

Melanoma is a tumor with strong immunogenicity. Compared with other tumors, it usually shows good lymphocyte infiltration [31]. The antitumor immune response is triggered by the release of tumor antigens and proinflammatory factors, which can promote DC maturation and T-cell activation. Tumor control after radiotherapy depends largely on the T cell response [32]. Our data analysis shows that radiotherapy can slightly induce the infiltration of CD8+ T cells, while radiotherapy combined with immunotherapy can significantly increase the infiltration of it, which is consistent with current research results [14]. CD8+ T cells are an important mediator of antitumor effects and play an important role in regulating the immune response against tumor cells [33-35]. CD8+ T cells can be activated by anti-PD-1 antibodies [36,37] and then migrate to the tumor microenvironment with the help of specific cytokines [38]. In addition to the resident CD8+ T cells in the tumor microenvironment, CD8+ T lymphocytes may migrate from other immune organs or the peripheral circulation. In this paper, the infiltration of CD8+ T cells into the irradiated tumor site in the combination treatment group was significantly higher than that in the other groups, and the degree of CD8+ T cell infiltration in the abscopal tumor site in the same group was significantly different. Radiation may affect the release of cytokines in the abscopal site and thus affect the migration of immune cells. It has been reported that radiation can enhance the release of factors that recruit immunosuppressive myeloid cells [39]. Radiotherapy also induced tumor cells to release colony-stimulating factor-1, leading to the expansion of myeloid-derived suppressor cells. Radiation not only increases the number of suppressive myeloid cells in irradiated tumors but also increases the number of suppressive myeloid cells in the peripheral blood, spleen, lymph nodes, and lungs [40]. Radiotherapy combined with anti-PD-1 treatment can significantly improve T cell infiltration in the irradiated field. Although the infiltration of T cells into the abscopal tumor was not as obvious as that in the irradiated tumor, the tumor volume of each site in the combination treatment group was significantly reduced. This shows that radiotherapy can improve the immunogenicity of tumors and be used to improve the effect of immunotherapy [41,42]. At the same time, the possibility that immunotherapy has a positive impact on the efficacy of radiotherapy was not ruled out. Current research results confirm this possibility [32,43]. In the immunotherapy alone group, the number of CD8+ T cells in the secondary tumor was slightly higher than that in the irradiated tumor, while the volume of the distant tumor in this group was significantly reduced. The effect on the distant tumor depended on the presence of T cells, which is consistent with the current research conclusion [44].

X-ray irradiation can not only enhance immune efficacy but also induce direct cell death. In our study, in the radiotherapy alone group, the volume difference between the irradiated and abscopal tumors was not significant, which showed that irradiation produced an abscopal effect and the same tumor volume-reducing effect on the primary and secondary tumors. In the mouse abscopal effect model we constructed, both the irradiated and abscopal tumors in the combination treatment group significantly regressed. Radiotherapy combined with immunotherapy could not only eliminate the irradiated tumor but also enhance the abscopal effect. A reasonable combination of radiotherapy and immunotherapy can overcome immunosuppression and lead to a strong antitumor T-cell response [45,46], thus producing stronger antitumor activity. This abscopal effect has been widely confirmed in immunogenic tumors [16,47-49].

In conclusion, we explored the root causes of different therapeutic effects from different perspectives, such as gene expression and immune infiltration, providing a new idea for improving therapy in melanoma patients and inducing the abscopal effect. Combination therapy could not only improve the immune microenvironment but also induce the abscopal effect and may have a positive impact on prognosis.

Statement of Ethics

This study protocol was reviewed and approved by The Animal Care and Use Committee of Changzhou Second People's Hospital.
Conflict of Interest

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

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Author Contributions

Conceptualization, MHW, JDL. Investigation and methodology, YFZ, XL, NL. Resources, ZQS, AMZ. Writing of the original draft, XL. Formal analysis, YFZ. All authors had finally approved the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00185.

References


Instructions for Authors

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Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions. For any persons who do not meet the above four criteria, they may be placed as contributors in the Acknowledgments section. Description of co-first authors or co-corresponding authors is also accepted if the corresponding author believes that their roles are equally contributed. After the initial submission of a manuscript, any changes in authorship must be explained by a letter to the Editor-in-Chief from the authors concerned. This letter must be signed by all authors of the paper. Copyright transfer and conflict of interest disclosure forms must be completed by every author. ROJ does not correct authorship after publication unless a mistake has been made by the editorial staff.

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Authors should have obtained written informed consent from all participants prior to inclusion in the study, and copies of written informed consent should be kept for studies on human subjects. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author's institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

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

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

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

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Type of study</th>
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The statement should be included in the Materials and Methods section after the IRB approval. Identifying details of the participants should not be published in written descriptions and photographs. In cases where identifying details are essential for scientific purposes, the participant should have given written informed consent for the identifying information to be published, and it should be stated separately.

Waiver of the informed consent can only be granted by the appropriate IRB and/or national research ethics committee in compliance with the current laws of the country in which the study was performed, and this should be separately stated. It should be noted that manuscripts that do not contain statements on IRB approval and patient informed consent can be returned to the authors before the review process.
3. Statement of Human and Animal Rights

All studies on human subjects must be conducted according to the principles expressed in the World Medical Association Declaration of Helsinki. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. The name or initials of the patient should not be displayed, and the patient's identity should not be known when submitting photographs related to the patient. If there is a possibility that the patient's identity may be exposed, it should be stated that the patient has given written consent.

All studies involving animals must state that the guidelines for the use and care of laboratory animals of the authors' institution, or any national law, were followed.

All studies dealing with clinical trials should be registered on the primary national clinical trial registration site, such as Korea Clinical Research Information Service (CRIS, http://cris.nih.go.kr), other primary national registry sites accredited by World Health Organization or ClinicalTrials.gov (http://clinicaltrials.gov), a service of the US National Institutes of Health.

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

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

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

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This journal follows the data sharing policy described in “Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors” (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018, manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing statement as described below. Clinical trials that begin enrolling participants on or after January 1, 2019, must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published with the manuscript and updated in the registry record. All the authors of research articles that deal with interventional clinical trials must submit data sharing plan. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.
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The Research Ethics Committee of the Korean Society for Radiation Oncology covers ethical issues involved with research and publication. This committee is composed of one chairperson and the members of the committee. The director of the ethics committee acts as the chairperson of this committee. The members of the Research Ethics Committee include the vice president, the auditor, the directors of general affairs, research, and publication committees, and two directors without a portfolio of the society become ex officio. The members of this committee serve for a term of two years, and they may be reappointed.

If presented with convincing evidence of dual publication, fragmentation, plagiarism, fabrication, or theft of intellectual property in journals, the committee meeting will be held immediately for investigation. If evidence becomes available that the regulation has been breached, publication of the corresponding manuscript is immediately canceled and all authors, including the corresponding author, are banned from any publication in the ROJ published for the next three years. The investigation results of the committee meeting must be notified for immediate disciplinary measures and reported to the board of directors. Other issues that are not specified in this regulation abide by the decisions made by board members of the society, which conform with the Ethics Code of Science Technology set forth by the Korean Federation of Science Technology Societies.

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임핀지™는 PACIFIC 연구에서 5년 전체생존율(OS rate) 42.9%로, 장기적인 생존개선 이점을 나타냈습니다. ²

<table>
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<tr>
<th>No. at Risk</th>
<th>Months since Randomization</th>
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<tr>
<td>Durvalumab</td>
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<td>Placebo</td>
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**임핀지(durvalumab) 보험 적용 적용증**

1. PD-L1 발현 양성(아그리자) 비말이 1% 이상의 백혈 기반 동등 양성암방사선요법 2주기 이상 투여 후 절제 혹은 화학요법이 없는 만성백혈병성 이상의 임상적 안정(Stage III NSCLC)
2. 방사선요법은 54 Gy 이상, 항암화학요법은 2주기 이상의 항암요법 종류가 동일
3. 방사선요법은 54 Gy 이상, 항암치료학약용은 항암요법 종류가 동일
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**STUDY DESIGN**

The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage I, unresectable NSCLC, with a WHO performance score of 0 or 1. Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy, without progression, and the last irradiation dose was 42 days before enrollment. Tumor tissue collection was set in a prospective central registry for the study, representing the cancer patient populations in South Korea. The primary tumor tissue samples were collected and centralized, and patients were followed up for 6 months or until confirmed death. The study was sponsored by AstraZeneca Korea, the Korean branch of AstraZeneca. The study was ethical and scientifically sound, and the ethical review committee at Samsung Medical Center approved the study. The study was registered with ClinicalTrials.gov (ClinicalTrial.gov Identifier NCT02346125). The study was funded by AstraZeneca Korea.

**REFERENCES**


**PRESCRIBING INFORMATION**

Precautions

1. Concomitant corticosteroid therapy or concomitant chemotherapy should be avoided. If concomitant therapy is required, it should be carefully monitored and the treatment should be stopped as soon as possible. If corticosteroids are used, the dose should be reduced as soon as possible. If chemotherapy is used, the dose should be reduced as soon as possible. If corticosteroids are used, the dose should be reduced as soon as possible. If chemotherapy is used, the dose should be reduced as soon as possible.

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