The current status of space modulated radiotherapy

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Abstract

Various kinds of spacers have been developed in recent years, consequently enabling advances in intra-abdominal space modulated radiotherapy. Especially, biocompatible and bioabsorbable spacers seem beneficial. Among malignant tumors, pancreatic cancer exhibits the poorest prognosis and several treatment strategies have been attempted for this tumor. Particle therapies combined with chemotherapy have the potential to improve the outcomes of pancreatic cancer patients, and avoiding or reducing the toxicity of the treatment by the use of nonwoven fabric spacers seems to be effective for not only pancreatic cancer, but also other upper abdominal malignant tumors and pelvic soft tissue sarcomas by stopping the proton or carbon-ion beams and separating the normal tissues from the radiation field. Next-generation polyglycolic acid (PGA) spacers are currently under investigation for the purpose of reduction of adhesions.

1. Introduction

Spacer placement is a promising method designed to allow for an increased tumor dose while limiting exposure to the adjacent organs in various types of radiotherapies, including intensity modulated radiotherapy (IMRT), brachytherapy, and particle therapy. Several types of spacers have been reported, and these can be further categorized according to the placement sites and diseases for which they are used.

2. Types of spacers, gels, and non-woven fabrics

Previous studies on the use of bio-compatible agents as spacers for prostate cancer have reported methods involving injection of a layer of hyaluronic acid (HA) or other gels to separate the prostate from the rectum [1-7]. Prada et al. [1,2] reported injecting 3-7 mL of HA into the perirectal fat before rectal radiation therapy in high- or low-dose brachytherapy. The results of their study indicated that the injected HA did not migrate or change shape for almost one year. Similarly, Wilder et al. [3] reported that cross-linked hyaluronic gel could safely and effectively reduce the mean rectal dose. However, Daar et al. [4] reported degradation of HA within weeks of radiation exposure. Using a different approach, Susil et al. [5] demonstrated the potential efficacy of a synthetic polyethylene glycol–based hydrogel (DuraSeal; Confluent Surgical, Waltham, MA) as a prostate–rectum spacer. Additionally, Pinkawa et al. [6] reported similar results after injection of a different spacer gel (SpaceOAR System; Augmenix, Waltham, MA), and Noyes et al. [7] demonstrated that, using human collagen, the increased separation between the prostate and rectum resulted in a significant decrease in radiation exposure to the rectum during IMRT and was associated with no rectal toxicities. In these studies, however, the methods or agents reported were limited to prostate–rectum separation and may be difficult to use in other locations.

Surgically placed non-woven fabric spacers have been used in various types of malignancies and sites. The GORE-TEX sheet, the first nonwoven fabric to be applied as a spacer in the field of particle therapy, is a waterproof, breathable fabric membrane that has been widely used in permanent implants, including artificial blood vessels, for many years [8-10]. The use of this spacer allows the application of particle therapy in cases in which it may otherwise result in severe incurable damage to the adjacent organs, including for upper abdominal malignant tumors. Although the GORE-TEX spacer is useful during the period of particle therapy, it becomes a foreign body after the completion of the therapy [10]. While problems related to the presence of the GORE-TEX spacer may be avoided by removal during a second surgery, repeated operations might be associated with certain risks for the patient.

3. Particle therapy

Particle therapy has emerged as a promising treatment modality, exhibiting more focused effects on target tissues. Several systematic reviews on proton or carbon-ion therapy have discussed the extensive use of particle therapy to treat various malignant tumors, including chordoma, ocular melanoma, and prostate cancer [11-13]. In particular, several studies have indicated the efficacy of proton therapy for the treatment of hepatocellular carcinoma [14-17]. Komatsu et al. [17] demonstrated excellent results for hepatocellular carcinoma, with local control rates for tumors <50 mm of 95.5% and 94.5% for proton and carbon ion therapy, respectively, and these data are similar or superior to those reported with local ablative therapies [18]. At the same time, the local control rates achieved with proton and carbon ion therapy for tumors measuring 50–100 mm in greatest dimension were 84.1% and 90.9%, respectively. However, the utility of proton therapy for other upper abdominal malignant tumors has not been fully clarified. One possible reason is that it is difficult to deliver curative doses of radiation to treat upper abdominal tumors without damaging adjacent radiosensitive organs such as the duodenum, jejunum, and stomach. Komatsu et al. [8] also reported that, in the treatment of hepatocellular carcinoma, surgical spacer placement could maintain a safety margin from the gastrointestinal tract, and that full-dose particle radiotherapy could be achieved without serious toxicities. Ismael et al. [19] reported that, for patients with unresectable liver tumors, placement of a biologic mesh spacer enhanced the safety and efficacy of high-dose radiotherapy, providing a survival benefit via a delay in the time to progression compared to traditional treatments, with no significant short or long term gastrointestinal toxicity. Another reason seems to be that image guidance in this area is difficult, and organ motion due to breathing or peristalsis may alter the beam range [20].

4. Pancreatic cancer and spacer placement

Among several upper abdominal malignant tumors, pancreatic cancer has the poorest prognosis [21,22]. Although chemoradiation could be considered to achieve locoregional control, grade 3 or higher toxicity is observed in approximately 20-40% of patients who receive preoperative chemoradiation [23]. Recently, Terashima et al. [24] reported successful results by combining gemcitabine with proton therapy to treat locally advanced pancreatic cancer. In that study, the authors reported 1-year local progression-free and overall survival rates of 81.7% and 76.8%, respectively. These results were speculated to obtain from the use of a total dose of 67.5 Gy relative biological effectiveness (RBE) to the major part of the planning target volume (2.7 Gy [RBE] per fraction), while simultaneously limiting the dose to the gastrointestinal tract to a total of 45 Gy (RBE) (1.8 Gy [RBE] per fraction), suggesting that the planning target volume dose was higher compared with in other studies [25-26]. However, several months after completing the therapy, approximately 10% of the patients developed grade 3 or higher gastric ulcers [27]. In such cases, surgical placement of a spacer between the pancreas and stomach might be an effective option to reduce gastrointestinal toxicities while maintaining the same dose to the tumors. However, the disadvantages and risks of performing a surgical procedure should be carefully taken into account when considering placement of a spacer.

Recently, Shinoto and coworkers [28] reported that carbon-ion radiation therapy with concurrent full-dose gemcitabine was well tolerated and effective in patients with unresectable locally advanced pancreatic cancer. Stereotactic body radiation therapy (SBRT) is another novel therapeutic option to achieve local tumor control in the management of pancreatic cancer. SBRT delivers a higher biological effective dose to the tumor, with sharp dose escalation in a shorter treatment time course. The Stanford group reported the first study demonstrating the feasibility of a single-fraction SBRT (25 Gy) regimen for locally advanced pancreatic cancer [29]. Excellent local control rates were achieved; however, increased rates of late gastrointestinal toxicity were found in subsequent studies from the same group and in the study by Hoyer et al. [30,31]. Following these initial reports, SBRT delivered in 3-5 fractions has been investigated [32,33], and several retrospective studies have revealed similar local control rates and a lower incidence of high-grade toxicity as compared to those of single-fraction SBRT. Although there are currently no reports reporting the use of a spacer in SBRT, spacers might become a powerful supportive tool in SBRT as well, and future studies should investigate this further.

5. Pelvic chordoma and spacer placement

Chordomas are rare bone tumors that arise from remnants of the notochord [34-36]. They constitute 1–4% of all primary malignant bone tumors, with sacral chordoma accounting for 50% of all chordomas [34-35, 37]. Chordoma grows slowly [34-36] and show fewer metastases than other bone and soft-tissue tumors [38,39]; however, mortality is almost inevitable because of local disease progression [38,40]. Recently, several investigators have reported on the efficacy of carbon-ion radiotherapy for sacral chordomas, describing high local control rates and low toxicities [41]. Report demonstrating the usefulness of proton therapy for sacral chordomas has also been published [42]. Leronzo et al. [43] recently reported their clinical experience of silicon spacer placement performed in 6 patients with sacral chordoma undergoing carbon-ion radiotherapy, and spacer placement thus seems beneficial in proton or carbon-ion radiotherapy for sacral chordoma.

6. Generation of bio-absorbable nonwoven fabric spacers

The purpose of producing a bio-absorbable nonwoven fabric spacer is to overcome the problems associated with the non-absorbable GORE-TEX spacer [44], which might cause serious complications after the completion of particle therapy. On the other hand, although previous investigators have reported the usefulness of gel spacers for separation of the prostate and rectum [5-6], those spacers are inappropriate for the upper abdomen, which contains lots of free space. Therefore, at present, a nonwoven fabric bio-absorbable spacer is necessary and appropriate for the separation of the tumor and adjacent organs in upper abdomen malignancies.

The process of producing the nonwoven fabric involves entangling threads in three dimensions with a needle-punching process, along with other methods [45,46]. Spacer placement during radiotherapy is a promising method designed to allow an increased tumor dose while limiting radiation exposure to the adjacent organs. The spacer exhibits excellent properties related to bio-absorbability, bio-compatibility, thickness retention, and water equivalency according to physical and animal experiments [44]. Interestingly, in the abdomen of crab-eating macaques, the thickness of PGA spacer was maintained 8 weeks after placement [44].

The reason and advantage for the use of PGA to construct these nonwoven fabric spacers are that PGA is one of the most widely studied polymers and has excellent mechanical properties and biological affinity [47,48]. Historically, PGA has played a central role in surgery since its development as the first synthetic absorbable suture material in 1962 [49]. Moreover, PGA is absorbed 60–90 days after insertion in the body and is hydrolyzed without any phagocytosis, which results in a weaker immune response than that of absorbable organic sutures [50]. Especially, for medical applications, a major advantage of PGA as a biodegradable polymer is that its degradation product, glycolic acid, is a natural metabolite [45,51] that is nontoxic and can enter the tricarboxylic acid cycle, after which it is excreted as water and carbon dioxide, as well as in the urine [49,50].

7. Current status and future of space modulated radiotherapy

Recently, several clinical experiences and data of spacer placement in combination with particle therapy or radiotherapy have been reported [19,43,52]. However, for the placement of these spacers, surgery was performed and, to a certain extent, adhesion could not be avoided. Adhesions after surgery might lead to serious complications [53,54]; in pelvic and abdominal sites, these complications might lead to small-bowel obstruction, infertility, chronic pelvic pain, and difficulty with further surgical access. Therefore, in terms of the spacer placement, it is necessary to minimize adhesions between the spacer and surrounding organs. In our preclinical study, the efficacy and safety of the PGA nonwoven fabric spacer were investigated using several animal models [44]. The PGA spacer exhibited excellent biocompatible properties and minimum adhesion.

However, to further improve the efficacy of the PGA spacer, additional reduction of adhesions need to be accomplished. In our preclinical assessment, we adapted the Seprafilm, an absorbable membrane composed of sodium hyaluronate and carboxymethylcellulose.

The Seprafilm has been widely used and investigated for surgical use in both animal and human studies [55,56]. Surprisingly, we found that the Seprafilm combined with the PGA spacer reduced adhesion compared to use of the PGA spacer alone. The adhesion grade scoring evaluated using the adhesion grading scale showed that adhesion was significantly reduced between 2 and 8 weeks after the placement of the spacer (Figure 1) [57-59]. Moreover, microscopic analysis using hematoxylin-eosin and Masson's trichrome staining indicated that aggressive cell invasion and extensive self-assembled fibrin/collagen developed in the PGA spacer, possibly related to the adhesion process (Figure 2, left panels). On the contrary, such cell invasion was rarely observed in cases of PGA used in combination with the Seprafilm (Figure 2, right panels).

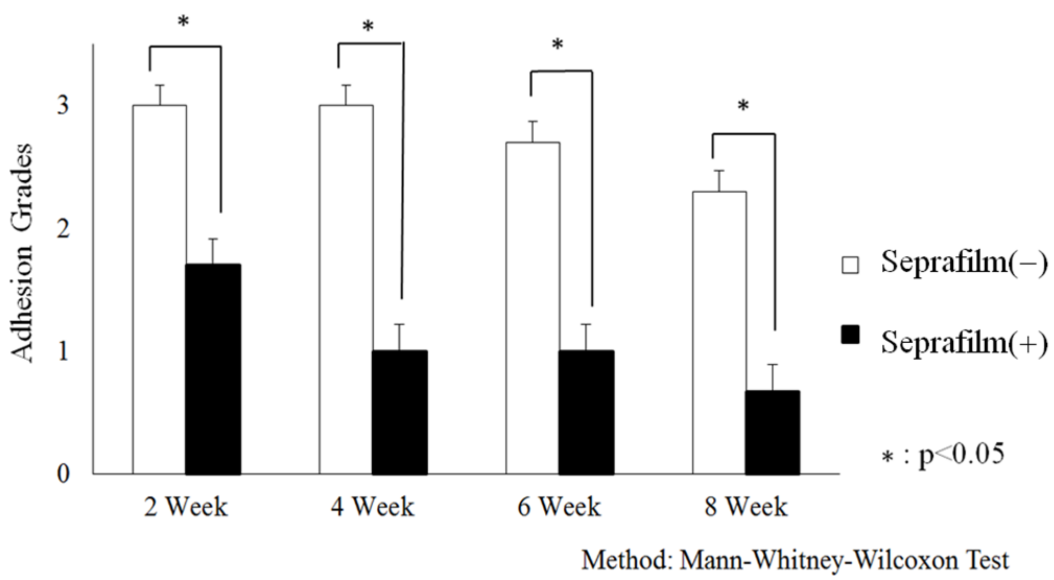

Figure 1. Macroscopic adhesion grades according to the use of Seprafilm and PGA spacer.

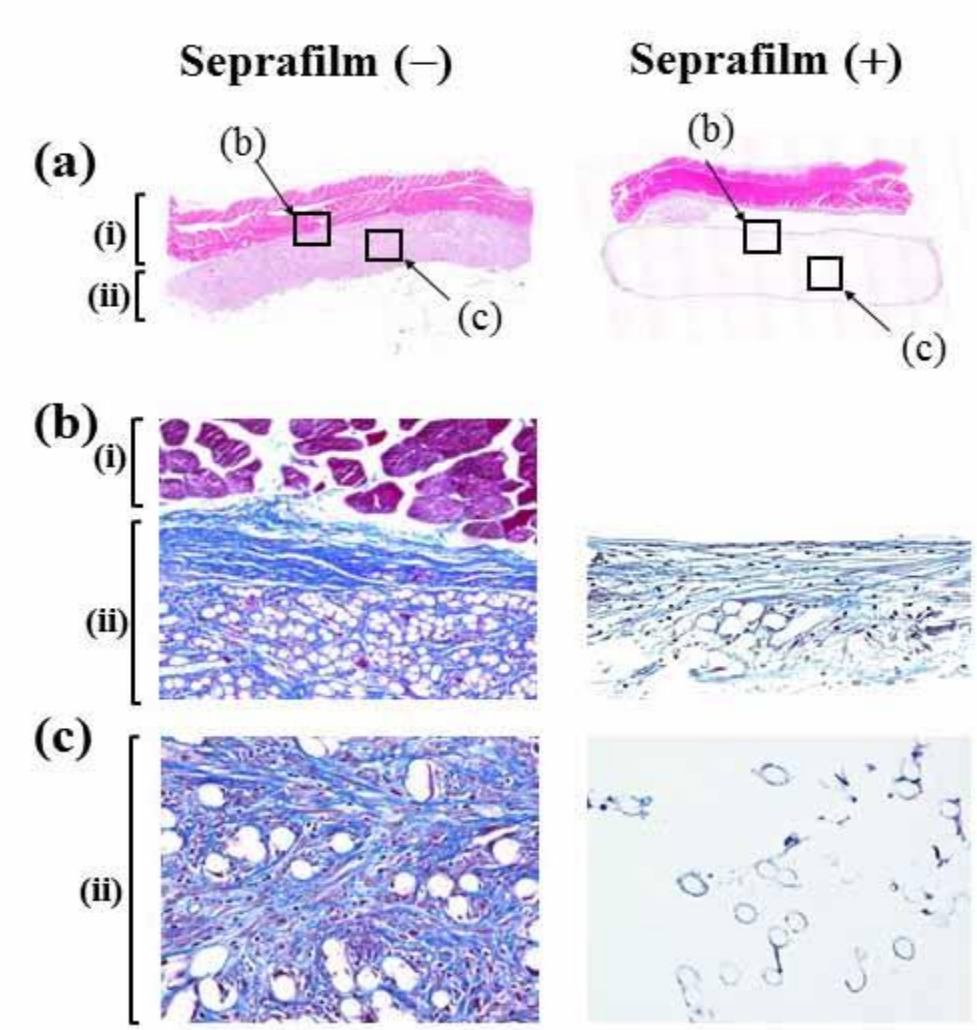

Figure 2. Microscopic features of the polyglycolic acid (PGA) spacer with or without Seprafilm at 2 weeks. (a) Hematoxylin-eosin stain. (b) Masson's trichrome stain outside the PGA spacer. (c) Masson's trichrome stain inside the PGA spacer. (i) Abdominal wall. (ii) PGA spacer with or without Seprafilm.

8. Conclusion

In conclusion, various kinds of spacers have been developed in recent years, and using these spacers, advances in intra-abdominal space modulated radiotherapy have been enabled. Biocompatible and bioabsorbable spacers seem beneficial; however, further evaluation is warranted in the clinical setting. For upper abdominal malignant tumors, application of the PGA nonwoven fabric spacer may be effective to stop proton or carbon-ion beams and to separate normal tissues from the radiation field. Next-generation PGA spacers are currently under investigation for the purpose of reduction of adhesions.

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