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Editorial

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Stereotactic body radiation therapy for pancreatic cancer: a potential ally in the era of immunotherapy?

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Pancreatic cancer (PC) is an aggressive malignancy with a poor prognosis. In 2022, 9,238 new cases of PC were expected to occur, and PC was ranked as the ninth leading primary site among the major cancers in Korea [1]. The incidence rates of PC have been on the rise and are predicted to increase over the next several decades, and PC is expected to be the fourth most common cause of cancer-related deaths by 2022 in Korea [1,2]. Curative surgical resection is the only chance for long-term survival; however, surgical resection is often limited due to many people being diagnosed at an advanced stage and the proximity of the pancreas to major vessels that cannot be replaced or removed.

Although the role of radiotherapy (RT) in PC has been controversial, it has been consistently proven that RT has a proven effect in controlling local disease [3,4]. Previous studies on PC showed that there were high rates of local recurrence or progression that led to the development of pain, gastrointestinal obstruction, bleeding, and other morbidities associated with the primary disease site, impairing the quality of life with chemotherapy and/or surgery alone [3,5]. Therefore, improving local control remains an important aim of RT in patients with PC, regardless of distant disease control. Moreover, RT has become an important modality by better systemic control with an improved chemotherapeutic regimen, and modern radiotherapy techniques with high-precision help local control in a multimodal setting with an acceptable side effect.

Stereotactic body radiotherapy (SBRT) is a modern RT technique that has various benefits compared with conventional RT and has been widely applied as a local therapy for the treatment of several types of malignancies [6]. SBRT enables conformal delivery of high radiation during a short period with reduced irradiation to surrounding normal tissues over conventional RT, and SBRT is considered to have different tumoricidal mechanisms [7,8]. SBRT for PC has been vigorously applied during the last decade for definitive or neoadjuvant aims due to the short treatment duration with limited acute toxicity, which is less disruptive to effective systemic treatment than chemoradiation therapy (CRT) [9]. A previous study that compared conventional CRT with SBRT showed that SBRT could be a feasible alternative to CRT for the treatment of PC [10].

In addition to these advantages of SBRT, it is worth noting that SBRT could promote antitumor immune response through various mechanisms, which could not be expected from conventional CRT [11-13]. However, because SBRT or immune checkpoint inhibitors (ICIs) alone is not sufficient to induce an effective immune response in PC, it could be a novel strategy to combine ICIs with SBRT to overcome resistance to immunotherapy, which means a shift from this "cold tumor" to "hot tumor" [8,13-15]. In the current study to be mentioned in this editorial, Reddy et al. [16] analyzed 68 pa-

tients with borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC) who received anti-programmed cell death-1 (PD-1) antibody and 5-fraction SBRT after chemotherapy to investigate the role of pre- and post-SBRT neutrophil-to-lymphocyte ratio (NLR).

After a median follow-up period of 10.7 months, the median overall survival (OS) after SBRT was 22.4 months, with a 2-year OS rate of 47.3%. The current study did not compare SBRT plus ICIs with SBRT alone, so the superiority of combination therapy with ICIs cannot be directly evaluated. However, given that most of the patients included in the current study had LAPC, the treatment outcome is considered promising compared to the previously reported treatment results of SBRT for PC with a median OS of 17 months from a meta-analysis [9]. In addition, one of the strengths of the present study is that all patients received standard multiagent chemotherapy, including FOLFIRINOX or gemcitabine/nab-paclitaxel regimen prior to SBRT and ICIs, given that previous studies included patients who received various chemotherapeutic regimens that could be less effective than the current standard regimens [9].

Recently, the results of a randomized phase 2 trial of SBRT plus pembrolizumab and trametinib versus SBRT plus gemcitabine for locally recurrent PC were reported [17]. A total of 170 patients were enrolled, and after a median follow-up of 13 months, SBRT plus pembrolizumab and trametinib showed a superior median OS (14.9 months vs. 12.8 months, $p = 0.021$). The authors concluded that SBRT could be a novel immunostimulatory strategy, and SBRT plus pembrolizumab and trametinib could be a new potential treatment option for patients with locally recurrent PC. Although the efficacy of SBRT plus ICIs for PC is not clearly defined, and more evidence is still needed, there are ongoing clinical trials being conducted that aim to assess the feasibility of SBRT combined with immunotherapy [15].

Meanwhile, Reddy et al. [16] showed that the post-SBRT NLR was a significant prognostic factor associated with OS on multivariate analysis. Patients with post-SBRT NLR ≥ 3.2 had a median OS of 15.6 months versus 27.6 months in patients with post-SBRT NLR < 3.2. The authors suggested that the change in NLR was largely due to a decrease in lymphocyte counts after SBRT. The difference in absolute lymphocyte counts was statistically significant compared to the pre-SBRT and post-SBRT values, but not for absolute neutrophil counts. Interestingly, a similar phenomenon has been reported in patients who receive CRT. Chadha et al. showed that post-CRT lymphopenia was associated with a poor prognosis in patients who received induction chemotherapy followed by CRT for LAPC [18].

There is a general consensus that multiple immune cell types exist in the tumor microenvironment (TME) and play an important role in cancer biology [19]. Neutrophils may act as tumor-promoting leukocytes, leading to a negative correlation between neutrophil density and patient survival. However, lymphopenia is associated with immune escape of tumor cells from tumor-infiltrating lymphocytes [20]. Therefore, the NLR might be related to the balance between the inflammatory pathway and antitumor immune function, and a high circulating NLR could be a biomarker of poor prognosis in various cancers [19]. Although the potential role of NLR for PC as a prognostic and predictive marker remains to be determined, NLR in PC could be a promising and convenient biomarker, as shown in a meta-analysis [21].

Reddy et al. [16] also showed that a larger target volume of SBRT correlated with a decreased lymphocyte count. In the present study, $\log_{10}$CTV (clinical target volume) had a negative correlation with the post-SBRT absolute lymphocyte count. The authors hypothesized that some RT-related factors, such as target volume or planning, might affect the outcome of patients after RT. These results are in line with those of previous studies. Wild et al. [12] analyzed serial total lymphocyte counts in patients with LAPC who received SBRT or CRT. They observed that SBRT was associated with significantly less lymphopenia than CRT after RT, implying that the RT technique could be associated with lymphopenia, which is related to survival. In addition, Chadha et al. [18] demonstrated that higher splenic doses were associated with the risk of developing severe lymphopenia after CRT in the analysis of dose-volume histogram parameters, including the mean splenic dose and percentage of the splenic volume received at least certain dose levels. These results may be related to the immunomodulatory effect of RT, but further studies are warranted to elucidate the precise mechanism.

The current study does not provide a clear answer for the role of SBRT in the immunotherapy era in the treatment of PC. However, it is interesting in that it provides a number of possibilities and discusses the need for further research on this subject. In addition to the already proven role of SBRT in PC, further research on SBRT must be conducted to answer these unsolved questions regarding the optimal conditions for the immunomodulatory effect of SBRT in terms of the optimal candidate, dose, volume, fractionation scheme, and timing associated with ICIs. As long as these questions remain, we must hold the belief that there is still hope for the role of RT in the treatment of this devastating disease.

Conflict of Interest

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

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