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doi: 10.6004/jnccn.2018.7112

Metastatic Anal Carcinoma: The Role of Radiotherapy

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Over the past 30 years, the incidence of invasive anal carcinoma in the United States has increased at a rate of roughly 2% per year.[1] Most patients present with locoregionally confined disease; distant metastases often involving liver, lung, or extrapelvic lymph nodes are found in only 5% to 8% of patients at initial presentation and in 10% to 20% of patients after curative locoregional treatment. Current standard treatment for locoregionally confined disease, developed based on many clinical trials, includes combined chemoradiation using 5-fluorouracil (5-FU)/mitomycin, capecitabine/mitomycin, or 5-FU/cisplatin. These approaches have resulted in a 5-year survival rate of 60% to 80%, and 60% to 75% local control with anal preservation.[2]

In contrast, only a few studies have addressed treatment approaches for patients with metastatic anal carcinoma (MAC). Based on several small-scale retrospective studies, including one case report, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Anal Carcinoma recommend using 5-FU/cisplatin, carboplatin/paclitaxel, or FOLFOX (5-FU/leucovorin/oxaliplatin) as first-line treatment for MAC.[2] The recently reported randomized, international, multicenter, phase II InterAACT study found that, compared with 5-FU/cisplatin, treatment with carboplatin/paclitaxel yielded more durable treatment response, superior overall survival (OS), and fewer serious adverse events.[3] In this study, treatment response rates were 59.0% for carboplatin/paclitaxel compared with 57.1% for 5-FU/cisplatin. Median OS was 20 months for carboplatin/paclitaxel versus 12.3 months for 5-FU/cisplatin (hazard ratio, 2.0; P=.014). Thus, this international study provides support for establishing carboplatin/paclitaxel as standard first-line treatment for MAC. For patients with metastatic disease that has progressed after first-line treatment, immune checkpoint inhibitors such as pembrolizumab and nivolumab are now recommended, and response rates of 17% to 24% have been reported.[4,5]

Clearly, room for improvement in treatment remains, raising the question for the role of radiotherapy (RT) in patients with newly diagnosed MAC. RT is generally thought to be palliative, and doses up to 30 to 37.5 Gy given over 10 to 15 fractions are often used to control disease locally for patients with a symptomatic bulky primary tumor.[2] The response rate to initial chemotherapy can be high and durable. Therefore, to control the primary disease in a more reliable way, radiation oncologists can reasonably treat primary tumors to a definitive dose (eg, ≥45 Gy). This is especially true for patients for whom chemotherapy has provided good control of systemic disease and/or who have potential for surgical resection of the metastases.

In this issue of the journal, Yuefeng Wang, MD, PhD, et al examine the role of definitive pelvic RT for patients with newly diagnosed stage IV MAC. The authors identified 437 patients who received chemotherapy alone and 1,020 patients who received pelvic chemoradiation (CRT) between 2004 and 2015 from the National Cancer Database (NCDB) and compared outcomes. At a median follow-up of 17.3 months, univariate and multivariate analyses revealed that pelvic CRT may be associated with better OS in patients with distant lymph node metastases and those with distant organ disease (propensity score–

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matched analysis of median survival and 2-year OS rate showed 21.3 months and 46% vs 15.9 months and 34% for CRT vs chemotherapy alone, respectively). To account for potential selection biases favoring administration of pelvic RT to patients with more favorable baseline characteristics, or "responders," sequential landmark analyses were used. These showed significantly greater OS at ≥1, ≥2, and ≥4 years in patients who received pelvic RT.

The authors should be commended for identifying 1,457 patients with an initial diagnosis of MAC to clarify the role of definitive pelvic RT. However, the authors note that this was largely a hypothesis-generating analysis and the results should be interpreted with caution. Indeed, although cancer registries, including the NCDB, are effective tools for studying cancer epidemiology and treatment, they provide only limited clinical information on treatment selection. Therefore, results of these studies are subject to selection biases. In this NCDB study, it is not clear how many of the 1,020 patients who received pelvic CRT actually underwent upfront induction chemotherapy. It is reasonable to assume that patients who received definitive RT (≥45 Gy) were those who did not experience disease progression after chemotherapy and/or were potential candidates for surgical resection to clear the metastases. Therefore, this group of patients was predisposed to have prolonged OS. Although propensity score–matched analysis and landmark analysis were conducted to address potential imbalance between the 2 patient groups and greater OS was confirmed in those with pelvic RT, essential confounding covariates were not available, such as extensiveness of metastasis, severity of individual comorbidities, and compliance with and response to the recommended chemotherapy. Thus, the validity of the conclusion is questionable, and the benefit of definitive RT in this study could certainly be overestimated. In general, stage IV patients with marked symptomatic primary disease will be given a palliative course of RT (<45 Gy) followed by full-dose systemic chemotherapy. The fact that OS between the groups treated with palliative RT plus chemotherapy or chemotherapy alone was similar further suggests a strong selection bias toward administration of definitive RT to patients with more favorable baseline characteristics.

Recently, Eng et al[6] reported encouraging results for patients with MAC. For certain patients, multidisciplinary management with systemic chemotherapy supplemented by a multimodality approach with curative intent, including surgery and RT, improved OS up to 53 months. This exceeds the previously recognized median OS of 12 to 20 months. Indeed, patients with metastatic cancer are no longer all considered incurable. Patients whose metastases are confined to a single organ, such as the liver or lung, or an isolated nodal area may experience long-term disease control after aggressive local management combined with successful systemic chemotherapy.

A retrospective study by Holliday et al[7] further confirmed that, for patients presenting with stage IV disease with metastases confined to para-aortic lymph nodes, treatment with curative-intent extended-field RT combined with chemotherapy could potentially improve overall outcome. A 3-year OS rate of 67% and 3-year disease-free survival rate of 42% were reported. Although no randomized study has been performed to define the benefit of ablative RT for patients with MAC, the SABR-COMET trial by Palma et al[8] and the study of local consolidative therapy in oligometastatic non–small cell lung cancer by Gomez et al[9] have shown a positive role for aggressive local therapy, including stereotactic ablative RT to improve survival in patients with oligometastatic breast, lung, colorectal, and prostate cancers. Some experts believe that with effective systemic treatment, patients with oligometastases may not experience disease progression or may only experience it in sites of initial disease. Therefore, these patients may be curable if all disease sites are eradicated.

Compared with surgical resection of primary or metastatic sites, RT provides the advantage of not only providing local control of the treatment site but also possibly eliciting immune responses to mediate regression of other disease sites (ie, the abscopal effect), especially when combined with systemic chemotherapy or immune checkpoint inhibitors. More importantly, RT preserves organs, and this will certainly help improve the quality of life for patients with anal cancer. Although the search for cure for patients with MAC continues, RT in addition to systemic chemotherapy and immunotherapy definitively plays an essential role in optimizing patient management.

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