Indications for neoadjuvant radiation in esophageal adenocarcinoma: Times are changing

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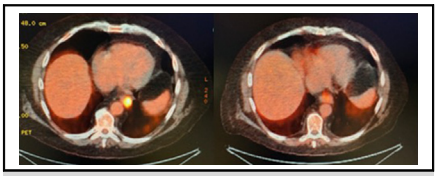
Radiation for resectable esophageal cancer was infrequently used before 2010.[1] This was largely due to the lack of proven benefit and surgeons' strong preference for upfront surgical resection.[2] There have been numerous trials comparing surgery alone with chemotherapy and radiation that either failed to accrue, such as the Cancer and Leukemia group B 9781, or failed to show a benefit across all patients.[3-6] This all changed with the landmark Chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) trial, which in 2012 showed a significant survival advantage with chemotherapy and radiation before surgery compared with upfront surgical resection. Although the survival advantage was strongest for squamous cell carcinoma, it was also significant for esophageal adenocarcinoma.[7] Now, more than a decade later, there have been numerous advances and changes to the way we provide radiation to the mediastinum. Additionally, the role of radiation in esophageal adenocarcinoma has been questioned, with changes and improvements in systemic and targeted therapies.



Esophageal cancer response to chemotherapy and radiation.

CENTRAL MESSAGE

The role of radiation in esophageal adenocarcinoma is rapidly evolving. Routine neoadjuvant chemotherapy/radiation was the standard of care for 20 years, but this approach is now an area of debate.

EVOLUTION OF ESOPHAGEAL RADIATION

Over the past 2 decades, there have been numerous advances and changes to the way we provide radiation to the mediastinum. At the time of the CROSS trial, the primary modality for esophageal radiation was 3-dimensional external beam radiation (3D-RT). This is an advance over 2-dimensional radiation, which was associated with substantial entrance and exit doses.[8] 3D-RT allows enhanced target and normal anatomy delineation and enables dose-volume histogram reporting. 3D-RT is still associated with acute toxicities, including esophagitis, nausea, fatigue, and cytopenia.

Intensity-modulated radiation therapy (IMRT) became the standard of care for the esophagus around 2016. This technology utilizes photon beams at many different angles. The intensity of the photon beams can be modified at different points in the treatment field, therefore decreasing exposure of normal tissue to high doses of radiation. The schedule and total dose for IMRT is the same as 3D-RT: 41.4 to 50.4 Gy in 23 to 28 fractions. There are mixed results when comparing IMRT and 3D-RT, but overall, IMRT has been associated with better long-term survival due to the reduction in noncancer-related deaths.[9]

The newest radiation technology being utilized for the esophagus is proton beam therapy (PBT). Protons are a particle and therefore have no exit dose. PBT also utilizes the proton Bragg peaks to allow for the highest radiation dose to be delivered only at the area of interest.[10] There was a recent randomized Phase 2B trial comparing PBT to IMRT. It was a 1:1 randomized trial of resectable esophageal cancer, 89% of which was esophageal adenocarcinoma. All patients received concurrent chemotherapy and a radiation dose of 50.4 Gy over 28 fractions. The total toxicity burden was calculated for each patient as a composite score of all toxicities experienced from all 3 modalities (chemotherapy, radiation, and surgery). The total toxicity burden for PBT was lower than IMRT with fewer cardiopulmonary toxicities and fewer postoperative complications.[11]

When comparing the current radiation therapies (3D-RT, IMRT, and PBT) there is no significant difference in cancer related outcomes: R0 resection rate, pathologic complete response, or disease-free survival. However, adverse events are lowest with PBT and highest with 3D-RT.[9,11]

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OMISSION OF NEOADJUVANT RADIATION

Some argue that radiation therapy is unnecessary for esophageal adenocarcinoma, particularly at the gastroesophageal junction. The current Society of Thoracic Surgeons/American Society for Radiation Oncology clinical guidelines agree that in patients with locally advanced adenocarcinoma of the esophagus or gastroesophageal junction, either neoadjuvant chemoradiation or neoadjuvant chemotherapy alone are reasonable to choose.[12] However, the current data are from small unblinded trials and meta-analyses with highly heterogeneous patient populations, neoadjuvant regimens, mixes of histology, and study designs. The most recent randomized control trial looking at this question compared the Medical research council adjuvant gastric infusional chemotherapy (MAGIC) and Fluorouracil plus leucovorin, oxaliplatin and docetaxel (FLOT) trial regimens to the CROSS trial regimen and found that neoadjuvant chemotherapy alone was not inferior to neoadjuvant chemotherapy and radiation with overall survivals of 55% versus 57% (hazard ratio, 1.03; 95% CI, 0.77-1.38). However, the neoadjuvant chemotherapy and radiation arm had significantly better R0 resection rates, higher percentages of ypN0 disease, and higher rate of complete pathologic response. There were also significantly fewer chemotherapy-related toxicities in the chemotherapy and radiation arm. The critics of this trial point out that the chemotherapy-alone arm shifted from the MAGIC regimen to the FLOT regimen midtrial with FLOT being the current standard of care.[13] Therefore, the Neoadjuvant trial in adenocarcinoma of the esophagus and esophagogastricl junction international study (Neo-AEGIS) trial may not be reflective of current clinical practice.

There are several ongoing clinical trials that aim to address the question of neoadjuvant chemotherapy versus chemotherapy and radiation for esophageal adenocarcinoma. A few of these trials include the Perioperative chemotherapy compared to neoadjuvant chemoradiation in patients with adenocarcinoma of the esophagus (ESOPEC) trial comparing FLOT versus CROSS with a 1:1 randomization. This trial has enrolled 438 patients with a primary end point of overall survival at 36 months. This trial is estimated to be completed during June 2024.[14] The Trial of preoperative therapy for gastric and esophagogastric junction adenocarcinoma (TOPGEAR) study is looking at gastric cancer but compares epirubicin, cisplatin, fluorouracil plus chemotherapy/radiation to epirubicin, cisplatin, fluorouracil alone. This trial has also completed enrollment of 574 patients and is awaiting 5-year survival data with an estimated study completion date of December 2026.[15] There are additional chemotherapy versus chemotherapy and radiation trials in gastric cancer (Neoadjuvant chemoradiotherapy vs chemotherapy with radical gastrectomy and adjuvant chemotherapy for advanced gastric cancer [NeoCRAG] and Neoadjuvant radiochemotherapy versus chemotherapy for patients with locally advanced, potentially resectable adenocarcinoma of the gastroesophageal junction [RACE]), which will shed more light of the risks and benefits of each approach.[16,17]

Esophageal adenocarcinoma with signet ring cell features deserves its own consideration. With current data, neoadjuvant chemotherapy with or without radiation continues to be the standard of care.[18] However, given the resistance of signet ring cells to systemic therapy and no difference in survival in gastric cancer with either before or after therapy, studies in esophageal cancer are warranted.[19] Ongoing clinical trials should capture patients with esophageal signet ring cell features, which will help with the decision for systemic therapy in these patients.

ADVANCES IN SYSTEMIC THERAPY

The debate of neoadjuvant chemotherapy versus chemotherapy and radiation will likely be overshadowed by the bigger questions in the field related to the role of radiation. These questions are: What does the addition of immunotherapy mean for the role of radiation? And, What about immunotherapy without radiation? There are data to suggest that conventional radiation therapy has the potential to be immunosuppressive. On the contrary, PBT may enhance the immunoadjuvant effects of radiation therapy and reduce the immunosuppressive mechanism.[20,21] There are no trials currently designed to look at the direct effect of immunotherapy and different radiation approaches in esophageal cancer. There are ongoing clinical trials looking at immunotherapy and radiation in patients with lung cancer. These results may improve our knowledge on the interaction of radiation and immunotherapy for thoracic malignancies overall.

There are numerous trials looking at the role of immunotherapy in esophageal and gastroesophageal adenocarcinoma. Some of these trials include radiation therapy, such as the Phase 2/3 study looking at nivolumab plus chemotherapy/radiation followed by esophagectomy with adjuvant immunotherapy.[22] This study should be resulting in 2024 and has the potential to change the standard of care for esophageal cancer. At the same time, there are numerous trials looking at immunotherapy for gastroesophageal and gastric cancer that do not include radiation. The key trials in this area are Assessing durvalumab and FLOT chemotherapy in resectable gastric and gastroesophageal junction cancer (MATTERHORN), Study of pembrolizumab plus chemotherapy versus placebo plus chemotherapy in participants with gastric and gastroesophageal junction adenocarcinoma (Keynote-585), and the Study of atezolizumab + FLOT versus FLOT alone in patients with GE/GEJ and high immune responsiveness (DANTE) trial.[23-25] These trials differ in their specific drug regimen, but all 3 include a

combination of perioperative chemotherapy with either a programmed cell death ligand 1 or programmed cell death protein 1 inhibitor. These trials are estimated to be completed in the next 1 to 3 years.

CONCLUSIONS

Radiation is likely to always have a role in treatment of esophageal adenocarcinoma, particularly in patients who are borderline surgical candidates. There will be data-driven answers to the question of neoadjuvant chemotherapy versus chemoradiation in the near future with numerous clinical trials reporting within the next few years. As we move the field of esophageal cancer forward, the question is no longer simply chemotherapy versus chemoradiation, but will focus on immunotherapy, targeted hormone therapy, and the role of biomarkers. It is truly an exciting time to be treating patients with esophageal cancer.

Conflict of Interest Statement

The author reported no conflict of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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