Indications for Neoadjuvant Radiation in Esophageal Adenocarcinoma: Times are Changing

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

Central Picture:
Esophageal cancer response to chemotherapy and radiation
Introduction

Radiation for resectable esophageal cancer was infrequently used in prior to 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 to chemotherapy and radiation that either failed to accrue, such as the CALGB 9781, or failed to show a benefit across all patients (3-6). This all changed with the landmark CROSS trial which resulted in 2012 showing a significant survival advantage with chemotherapy and radiation prior to surgery compared to upfront surgical resection. Although the survival advantage was strongest for squamous cell carcinoma, it was also significant for esophageal adenocarcinoma (7). Now over 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.

Evolution of esophageal radiation

Over the last two 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 3D external beam radiation (3D-RT). This is an advance over 2D 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, however, 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, 41.4Gy-50.4Gy in 23-28 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 non-cancer 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 IIIB 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 50.4Gy over 28 fractions. The total toxicity burden was calculated for each patient as a composite score of all toxicities experienced from all three 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).

Omission of neoadjuvant radiation

Some argue that radiation therapy is unnecessary for esophageal adenocarcinoma, particularly at the gastroesophageal junction. The current STS/ASTRO/ASCO 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 is 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 MAGIC and FLOT trial regimens to the CROSS trial regimen and found that neoadjuvant chemotherapy alone was not inferior to neoadjuvant chemoradiation with overall survivals of 55% vs 57%, HR 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 mid trial with FLOT being the current standard of care (13). Therefore, the Neo-AEGIS trial may not be reflective of current clinical practice.

There are several on-going 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 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 in June of 2024 (14). The TOPGEAR study is looking at gastric cancer but compares ECF plus chemotherapy/radiation to ECF 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 (Neo-CRAG and 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 pre or post therapy, studies in esophageal cancer are warranted (19). On-going 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 as 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 is 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 on-going clinical trials looking at immunotherapy and radiation in lung cancer patients. 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 II/III study looking at Nivolumab plus chemotheraphy/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 which do not include radiation. The key trials in this area are MATTERHORN, Keynote 585 and the DANTE trial (23-25). These trials differ in their specific drug regimen, but all three include a combination of peri-operative chemotherapy with either a PD-L1 or PD-1 inhibitor. These trials are estimated to be completed in the next one to three years.

Conclusion

Radiation is likely to always have a role in 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 hormonal therapy, and the role of biomarkers. It is truly an exciting time to be treating patients with esophageal cancer.

References


Central picture: Esophageal cancer response to chemotherapy and radiation