

# Treatment of Early-Stage Esophageal Adenocarcinoma

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## Abstract

Although T2,N0,M0 esophageal adenocarcinoma is grouped with other locoregional disease by NCCN, no consensus exists about how it should be treated. One of the inherent complexities of treating T2,N0,M0 esophageal adenocarcinoma is the inaccuracy of the clinical staging. In addition, conflicting evidence exists about whether neoadjuvant therapy adds any benefit to esophagectomy. A 52-year-old patient recently seen at the Robert H. Lurie Comprehensive Cancer Center illustrates the complexity of these issues. (*JNCCN* 2013;11:640–644)

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### Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the rationale for the management of patients with early-stage esophageal adenocarcinoma
- Identify appropriate mechanisms for the staging of early-stage esophageal adenocarcinoma

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## Early-Stage Esophageal Adenocarcinoma

An estimated 17,460 new cases of esophageal cancer occurred in 2012,<sup>1</sup> and the incidence of adenocarcinoma of the distal esophagus specifically is increasing at a rapid rate. The prognosis of patients with esophageal adenocarcinoma is poor, despite esophagectomy, and studies have sought to determine the appropriate treatment for early-stage esophageal adenocarcinoma. However, the ideal treatment of localized esophageal adenocarcinoma is still controversial.

### Patient Case

A 52-year-old man with a past medical history of ulcerative colitis presented to Robert H. Lurie Comprehensive Cancer Center regarding his recently diagnosed adenocarcinoma of the esophagus. The patient first noted dyspepsia a few months before diagnosis and was given a proton pump inhibitor, which relieved his symptoms temporarily. He denied any hematemesis, dysphagia, or weight loss. He subsequently had an esophagogastroduodenoscopy (EGD) after his symptoms returned. The EGD showed a 4- to 5-cm ulceration in the distal esophagus. The biopsy results showed poorly differentiated adenocarcinoma. An endoscopic ultrasound (EUS) showed a T2,N0 lesion at the gastroesophageal junction, and a CT scan showed soft tissue fullness in the distal aspect of the esophagus, which involved the gastroesophageal junction area and several mildly enlarged lymph nodes in the epigastric area. A PET scan showed hypermetabolic activity only in the distal esophagus. The patient's tumor was staged as T2,N0,M0, IIA, grade III. His past medical history is limited to ulcerative colitis, for which he takes mesalamine. He has no significant family history of cancer, is a never-smoker, drinks alcohol rarely, and is fairly active. His physical examination is unremarkable, with no neck masses appreciated and no cervical or axillary lymphadenopathy; his body mass index is 22 kg/m<sup>2</sup>. He has an ECOG performance score of 0.

### Discussion

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Esophageal and Esophagogastric Junction Cancers group patients with T2,N0 disease with other locoregional disease (stages I–III).<sup>2</sup> The guidelines recommend the

following options for patients with stage I–III esophageal cancer:

- Perioperative chemotherapy
- Definitive chemoradiation
- Preoperative chemoradiation followed by esophagectomy
- Esophagectomy

Starting with perioperative chemotherapy, a 2006 randomized trial focused on patients with resectable adenocarcinoma of the stomach (74%), esophagogastric junction (EGJ) (11.5%), or lower esophagus (14.5%).<sup>3</sup> Patients who underwent perioperative chemotherapy with etoposide, cisplatin, and 5-FU (ECF) had a significantly greater 5-year survival rate (36% vs 23%;  $P=.009$ ) and progression-free survival (hazard ratio for progression, 0.66;  $P<.001$ ) than the group that underwent surgery alone.

Much of the evidence for definitive chemoradiation relates to squamous cell carcinoma, whereas much more limited information is available regarding definitive chemoradiation in adenocarcinoma. A phase III, prospective, randomized trial compared combined chemoradiation with radiation alone in patients with squamous cell carcinoma (88%) or adenocarcinoma (12%) of the esophagus.<sup>4</sup> The chemoradiation group received 5-FU and cisplatin. The combined modality treatment group had a significantly greater median survival compared with the radiation-alone group (12.5 vs 8.9 months;  $P<.001$ ), with an increase in hematologic and upper aerodigestive toxicities. The NCCN Guidelines recommend that patients who have persistent local disease despite definitive chemoradiation be considered for salvage esophagectomy or palliative therapy.<sup>2</sup>

Conflicting evidence exists about the benefits of neoadjuvant chemoradiation in locally advanced esophageal cancer. The first randomized study limited to patients with esophageal adenocarcinoma that compared surgery alone versus neoadjuvant chemoradiotherapy followed by surgery showed a benefit from multimodality treatment.<sup>5</sup> The patients who received combined modality therapy had a significantly improved median survival compared with those who underwent surgery alone (16 vs 11 months;  $P=.001$ ). One issue raised, however, was the low rate of survival in the patients treated with surgery only, which might have led to a disproportionate difference between the groups.

Polish and Mulcahy

A meta-analysis conducted in 2002 included 9 randomized controlled trials that focused on neoadjuvant chemoradiotherapy.<sup>6</sup> The odds ratio comparing neoadjuvant chemoradiation versus surgery alone was 0.66 for 3-year survival ( $P=.016$ ). A more recent study focused on patients with resectable (T2–3,N0–1,M0) esophageal or EGJ tumors (75% adenocarcinoma, 25% squamous) and randomized them to either neoadjuvant chemoradiation or surgery alone.<sup>7</sup> The median survival in the combined modality group was 49 months versus 26 months in the surgery alone group. However, other studies have not shown a benefit to adding neoadjuvant therapy to esophagectomy. One randomized trial compared neoadjuvant chemoradiotherapy with cisplatin and 5-FU versus surgery alone in patients with esophageal cancer (all histologies). The study, which was underpowered, showed that although there was a trend toward improved progression-free survival and overall survival in the squamous cell cancers, no difference was seen in adenocarcinomas.<sup>8</sup>

For patients with resectable gastroesophageal adenocarcinoma, postoperative chemoradiotherapy is another option. In the definitive Intergroup trial, patients with resected adenocarcinoma of the stomach or gastroesophageal junction (20% of patients) were assigned to either surgery plus postoperative chemoradiotherapy with 5-FU and leucovorin or surgery alone.<sup>9</sup> The patients who were given trimodality treatment had an overall survival of 36 months compared with 27 months in the patients treated with surgery alone ( $P=.005$ ). The authors point out that the survival in the surgery-alone arm was commensurate with that seen in other studies.

Although all stage I–III esophageal cancers are grouped together, T2,N0 tumors present unique challenges, because they fall into a gray zone when it comes to appropriate treatment. Patients with T1,N0 esophageal cancer can be treated with surgery alone. However, it is generally agreed that patients with T2,N1 disease should be treated with combined modality therapy. The treatment of patients with T2,N0 esophageal cancer is more controversial, however, and a dearth of randomized trials exists to help determine the proper treatment for these patients.<sup>10</sup>

One of the inherent complexities of treating patients with T2,N0 esophageal cancer is that the clinical staging is frequently inaccurate despite

the use of PET and EUS. EUS plays a critical role in staging for esophageal cancers, and also has prognostic significance. One study found that EUS T stage is an independent prognostic indicator; patients with EUS stage T1–2 disease had a significantly better disease-free survival than those who had EUS stage T3 disease after surgical resection (odds ratio, 2.9;  $P=.001$  for univariate analysis).<sup>11</sup> Another study found that patients with EUS stage T1–T2,N0 disease who were not upstaged (56%) after receiving surgery alone had an 89.8% 5-year overall survival, compared with 39.9% for the group that was upstaged ( $P\leq.001$ ).<sup>12</sup> Although clear differences exist between the natural history of T2 and T3 esophageal cancers, the accuracy of EUS is not as good for T1 and T2,N0 lesions, because it is for more advanced lesions. Studies have found a high rate of both understaging and overstaging in T2,N0 esophageal adenocarcinoma. One study found that 55% of patients with T2,N0 esophageal cancer had unsuspected nodal disease at the time of surgery.<sup>9</sup> Another study found that 55% of patients with T2,N0 disease were overstaged, 32% were understaged, and only 13% of patients were staged accurately.<sup>13</sup>

The accuracy, or lack thereof, of clinical staging has treatment implications. Once a patient has received neoadjuvant therapy, pathologic staging is no longer possible, and thus treatment decisions will be dictated by clinical staging. Furthermore, because of the prevalence of overstaging, patients who receive neoadjuvant therapy may undergo unnecessary chemotherapy and be exposed to its subsequent complications.

In addition, conflicting evidence exists regarding whether patients with T2,N0 disease should be treated with esophagectomy alone or should receive neoadjuvant or adjuvant therapy. One retrospective study focused on 49 patients with adenocarcinoma (90%) or squamous (10%) cancer of the esophagus who were staged as T2,N0,M0 and received neoadjuvant chemoradiation.<sup>14</sup> The study found that the 5-year rates for overall and disease-free survival were 64% and 58%, respectively. The authors acknowledged that the lack of evidence regarding T2,N0,M0 disease makes their results impossible to compare with those of other studies. Still, they conclude that the findings support the use of multimodality therapy in patients with T2,N0,M0

## Early-Stage Esophageal Adenocarcinoma

esophageal cancer, and indicate the need for additional research in this area.

Other studies, however, have found that patients treated with multimodality therapy actually have a worse outcome than those treated with surgery alone. A randomized controlled phase III trial of patients with stage I or II esophageal cancer compared treatment with surgery alone versus neoadjuvant chemoradiotherapy.<sup>15</sup> Interim analysis found that 30-day mortality rates were higher in the combined modality group (7.3% vs 1.1% in the surgery group;  $P=.054$ ), with no improvement in overall survival compared with the surgery-alone group.

In a retrospective, single-institution study of 61 patients with T2,N0,M0 esophageal cancer, 45 underwent surgery alone, 8 underwent surgery and postoperative adjuvant therapy, and 8 underwent induction therapy followed by surgery.<sup>13</sup> Patients who received induction therapy actually had worse 5-year survivals compared with those in the other groups ( $P=.05$ ), with 1 of the 7 deaths caused by treatment toxicity and the other 6 related to recurrent cancer. Taken together with the evidence of inaccurate staging, the authors argued that patients with T2,N0,M0 esophageal cancer should undergo surgery first with lymphadenectomy. If these patients are found to be understaged, they should receive adjuvant therapy, whereas those found to be accurately staged would have “acceptable survival with surgery alone.” One of the benefits of this approach is that it eliminates the toxicity of adjuvant or neoadjuvant therapy for patients who ultimately require only an esophagectomy.

The NCCN Guidelines have included a similar approach for patients with resected T2,N0 esophageal and EGJ adenocarcinoma.<sup>2</sup> Esophagectomy alone can be considered for these patients, and postoperative treatment is determined by the pathologic stage (for an R0 resection)

- pT1,N0 or pT2,N0: observation
- pT3,N0: observation or chemoradiation
- Node-positive: chemoradiation

Of the 4 options discussed, neoadjuvant chemoradiation therapy is the most commonly used treatment for patients with resectable esophageal cancer. Although some studies have shown no benefit, the preponderance of data shows that multimodality therapy is preferred to surgery alone. In addition, patients are more likely to receive the full

course of chemotherapy if it is given neoadjuvantly as opposed to after surgery. The NCCN Guidelines indicate that the preferred approach for localized esophageal and EGJ adenocarcinoma is preoperative chemoradiation. Importantly, radiation and chemotherapy are recommended to be given concurrently.<sup>2</sup>

### Patient Case Approach

As for the 52-year-old man with T2,N0,M0 adenocarcinoma, the authors discussed the several different options for treatment. A primary consideration was the poorly differentiated nature of his malignancy. The AJCC takes grade into account in its staging of esophageal adenocarcinoma, and the patient's poorly differentiated tumor upstages him from IB (if his tumor were lower grade) to IIA. Therefore, the authors asked the patient to consider neoadjuvant therapy. Despite conflicting evidence, many studies indicate improved survival with neoadjuvant therapy. Although the prevalence of overstaging puts him at risk for receiving chemotherapy unnecessarily, he would likely tolerate the chemotherapy well given his young age. The authors indicated that chemotherapy would be given concurrently with radiation therapy. The patient subsequently met with representatives from radiation oncology and surgery. He agreed to neoadjuvant chemoradiation therapy followed by esophagectomy, and initiated treatment at an institution closer to his home.

### Future Directions

Studies have examined targeted therapy options in patients with gastroesophageal cancer. One potential target is HER2, which is expressed in roughly 20% of these cancers. A 2010 phase III, randomized, controlled trial focused on patients with advanced gastric or gastroesophageal junction cancer who overexpressed HER2.<sup>16</sup> These patients were randomized to chemotherapy alone or chemotherapy plus trastuzumab. Patients who were given trastuzumab along with chemotherapy had an overall survival of 13.8 months compared with 11.1 months in patients who received chemotherapy alone ( $P=.0046$ ).

Trastuzumab was subsequently approved in combination with chemotherapy for patients

Polish and Mulcahy

with metastatic gastric or gastroesophageal adenocarcinoma who overexpress HER2 and have not received prior treatment. The role of trastuzumab with chemoradiation in patients with HER2-positive locally advanced esophageal adenocarcinoma is being studied in RTOG 1010.

Another area of research is the role of PET scans after initiation of treatment. Studies have shown that response to therapy as indicated by PET scans may be predictive of a patient's prognosis.<sup>17</sup> What is not known is whether treatment should be altered based on the findings from the PET.

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## Posttest Questions

1. True or False: The NCCN Guidelines indicate that the preferred approach for localized esophageal and EGJ adenocarcinoma is preoperative chemoradiation.
2. Which of the following options is recommended by the NCCN Guidelines for patients with stage I–III esophageal cancer?
  - a. Perioperative chemotherapy
  - b. Definitive chemoradiation
  - c. Preoperative chemoradiation followed by esophagectomy
  - d. Esophagectomy
  - e. All of the above
3. True or False: Postoperative treatment is determined by the pathologic stage for patients with completely resected T2,N0 esophageal and EGJ adenocarcinoma.

