

**EDITORIAL COMMENT**

# Cardiovascular Concerns in the Management of Esophageal Cancer Patients\*



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## TREATMENT APPROACH FOR LOCALIZED ESOPHAGEAL CANCER

Esophageal cancer is a major global health problem, with >600,000 patients diagnosed in 2020, and is 1 of the top 10 cancer types diagnosed in patients worldwide.<sup>1</sup> The mortality associated with esophageal cancer is high, but about 50% of patients present with localized disease, for which the goal of treatment is cure.<sup>2</sup> The current treatment standard for patients with localized disease, either adenocarcinoma or squamous cell carcinoma, is weekly carboplatin and paclitaxel chemotherapy for 5 weeks with concurrent radiation therapy.<sup>3</sup> The CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) trial demonstrated that neoadjuvant carboplatin, paclitaxel, and radiation therapy followed by surgical resection, compared with surgery alone, resulted in superior median overall survival (49.4 months vs only 24.0 months; HR: 0.657;  $P = 0.003$ ). From this point forward, neoadjuvant chemoradiation with a carboplatin and paclitaxel chemotherapy backbone became the treatment standard.

A total of 357 patients were included in the CROSS trial, 171 of whom received chemoradiation followed by surgery and 186 of whom underwent surgery alone. In the chemoradiation group, 21% of patients experienced cardiac complications (arrhythmia,

myocardial infarction, or left ventricular failure) compared with 17% of patients in the surgery-alone group. These events occurred in the postoperative period and not during the chemoradiation period.

Cardiac complications are known to occur in patients undergoing esophagectomy. The most common complication is atrial fibrillation, which has been reported as occurring in the postoperative period in 11.5% to 22% of patients. Myocardial infarction has been reported as occurring anywhere from 1.1% to 3.8% of patients.<sup>4</sup> As many patients undergoing esophagectomy require neoadjuvant chemoradiation, one key question is whether this treatment additionally contributes to cardiovascular complications. Given the inherent nature of the disease, with a primary tumor blocking the esophagus in a number of cases, resulting in significant dysphagia, it is not uncommon for patients to become volume depleted secondary to poor oral intake. This can then be further exacerbated during the course of radiation by the development of radiation esophagitis. The question of how these clinical features further contribute in the setting of underlying cardiovascular disease is unknown, as is the role for optimization of cardiovascular status prior to initiation of complex cancer treatment.

## CARDIOVASCULAR DISEASE IN THE MANAGEMENT OF PATIENTS WITH LOCALIZED ESOPHAGEAL CANCER

In the present study by Søndergaard et al,<sup>5</sup> the investigators sought to assess the prevalence of cardiovascular disease in the specific population of patients with localized esophageal cancer who would be undergoing treatment with definitive chemoradiation or chemoradiation plus surgery. They additionally aimed to determine the frequency and

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characterization of cardiovascular events that occurred in these patients during and after treatment. To achieve this, 55 patients were enrolled and, prior to initiation of cancer therapy, underwent a comprehensive cardiovascular evaluation inclusive of physical examination, cardiac and medication history, 12-lead electrocardiography, comprehensive trans-thoracic echocardiography, and a symptom-limited, semisupine cardiopulmonary exercise test with assessment of peak oxygen consumption. Patients were then monitored for the development of cardiovascular events during chemotherapy, radiation, and surgery, with cardiovascular events defined as major adverse cardiac events as per the American Heart Association and American College of Cardiology (transient ischemic attack, imaging-verified new stroke, unstable angina, or heart failure or cardiomyopathy requiring an urgent visit or hospitalization)<sup>6</sup> or a grade  $\geq 3$  toxicity per the Common Terminology Criteria for Adverse Events version 4.0.<sup>7</sup> These included arrhythmia, thromboembolic events, and pericardial effusion requiring pericardiocentesis.

On the basis of an initial assessment, 33% of patients were found either to have undiagnosed cardiovascular disease or to be receiving inadequate treatment. Moreover, measures of cardiovascular function and fitness were mildly reduced. According to sex-specific cutpoints, 27% of men and 17% of women had an abnormal left ventricular ejection fraction. Fifty-one percent had low global longitudinal strain. A measure of cardiopulmonary fitness, peak oxygen consumption, was 87% of predicted. During the 90-day follow-up period, 15 cardiovascular events occurred among 13 patients, with 4 of these patients being those who entered the study with undiagnosed cardiovascular disease. Overall, the 90-day event rate was 24%. A univariable analysis identified left atrial volume index  $\geq 34$  mL/m<sup>2</sup> and pre-existing atrial fibrillation as features significantly associated with the development of major cardiac adverse events during the treatment period (HRs: 3.59 and 4.35, respectively).

Cardiovascular disease is common and increases with age and among patients with cancer,<sup>8</sup> and as such, it is not surprising that a baseline level of undiagnosed and/or inadequately managed cardiovascular disease was identified among the study patients. There were also some limitations to the present study. One key distinction not made by the investigators is when during treatment cardiovascular events occurred: during the chemoradiation portion of the study or in the postoperative period. Cardiovascular complications are known to occur in the postoperative

setting for these patients and are relatively uncommon during the course of chemoradiation. Additional detail in this regard would be informative and could additionally aid in determining by which stage of treatment cardiovascular status needs to be optimized.

## IMPLICATIONS IN THE MANAGEMENT OF PATIENTS WITH ESOPHAGEAL CANCER

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Clearly this study sheds important light on the fact that a significant number of patients diagnosed with localized esophageal cancer have concomitant undiagnosed or inadequately managed cardiovascular disease. The increased risk for cardiovascular complications, particularly in patients undergoing platinum-based therapies with potential vascular and cardiometabolic effects,<sup>9</sup> radiation, and esophagectomy as part of their cancer management, does suggest that more should be done at the time of cancer treatment initiation to manage cardiovascular disease in an effort to overall improve cancer treatment-related morbidity and mortality.

One improvement that has been made in recent years is the use of proton beam radiotherapy as opposed to intensity-modulated radiation therapy (IMRT) in the management of localized esophageal cancer. Comparison of these treatment modalities demonstrates an overall improvement in toxicity without sacrificing progression-free survival outcomes.<sup>10</sup> In a recent trial of 145 patients receiving chemoradiation, with 72 receiving IMRT and 73 receiving protons, atrial fibrillation, myocardial infarction, and asymptomatic pericardial effusion were seen in 5, 1, and 6 patients, respectively, in the IMRT group compared with 1, 0, and 2 patients in the proton group. During the postoperative period, atrial fibrillation and stroke were seen in 7 and 1 patients, respectively, in the IMRT group compared with atrial fibrillation in only 2 patients in the proton group.

Progress is being made in the use of more refined radiation techniques that do spare the heart and hence overall reduce any associated cardiotoxicity. Esophagectomy continues to be the element of this treatment paradigm that is associated with the greatest cardiovascular risk. Given the high prevalence of undiagnosed and inadequately managed cardiovascular disease as well as a worsening cardiovascular outlook in the younger part of the population,<sup>11</sup> instituting more regular cardiovascular assessment into the multidisciplinary paradigm for management of patients with localized esophageal cancer is very reasonable.

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