

## EDITORIAL

# Endoscopic Resection for Early-Stage Esophageal Cancer, Are We There for Squamous As Well?

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**Superficial esophageal squamous cell cancer (SESCC) is often managed with esophagectomy with or without chemoradiotherapy. Esophagectomy has a significant complication rate and is not an option for many patients. In the current issue, a retrospective single center study evaluated 66 patients with SESCO. With endoscopic resection followed by adjuvant chemoradiotherapy, the reported 1-, 3- and 5-year overall survival rates were 98%, 87% and 75% respectively, comparable to survival rates after esophagectomy or definitive chemoradiotherapy. This study suggests a key role for endoscopic management in SESCO, and provides important data on the combination of endoscopic management plus adjuvant chemoradiation.**

*Clinical and Translational Gastroenterology* (2017) 8, e130; doi:10.1038/ctg.2017.56; published online 14 December 2017

Esophageal carcinoma remains the 8th leading cancer worldwide and the 6th leading cause of cancer death.<sup>1</sup> Esophageal cancer is widely prevalent in Southern and Eastern Africa and Eastern Asia and less prevalent in Western and Middle Africa and Central America.<sup>2</sup> While esophageal adenocarcinoma (EAC) has been increasing in the United States,<sup>3</sup> squamous cell carcinoma (SCC) has become less common and now accounts for fewer than 30% of cases of esophageal cancer in the United States and Western Europe.<sup>4</sup> In the US, EAC incidence has increased at the rate of 5.7% year between 1973 to 2011.<sup>5</sup> However globally, in areas with a high prevalence of Esophageal Cancer, SCC of the esophagus is more common than EAC,<sup>4</sup> where >90% of carcinoma is of squamous histology.<sup>6</sup>

The treatment of Esophageal Cancer largely depends upon the stage at diagnosis. The depth of cancer invasion and lymph node (LN) involvement are the critical determinants of eligibility for endoscopic management. A recent review examining resected early carcinoma for both EAC and SCC found that the risk of LN metastasis in early T1a stage cancer is 0%; however once cancer progresses to T1b stage, the risk of LN metastasis has ranged from 4–46%.<sup>7</sup> Other studies reported a LN involvement rate of 0 to 2% in EAC and 7.7% in SCC<sup>8,9</sup> for mucosal disease. In submucosal cancer when classified by depth of involvement of submucosa to SM1 (superficial 1/3), SM2 (middle 1/3) and SM3 (deepest 1/3), risk of LN involvement increases from 0–21% in SM1 disease to 43–67% in SM3 disease.<sup>10,11</sup> The current NCCN guidelines

recommend an endoscopic approach as preferred for Tis and T1a esophageal cancers, and endoscopic resection or esophagectomy for superficial T1b cancers in medically fit patients.<sup>12</sup> Endoscopic treatment for local disease control in addition to chemoradiation for submucosal (T1b) SCC has been reported.<sup>13,14</sup> These studies also found a reduction in side effects with the approach, attributed to a reduced dose of radiation.<sup>14</sup> A study comparing endoscopic mucosal resection (EMR) with chemoradiation to esophagectomy for superficial SCC (T1a and T1b – SM1) revealed comparable overall survival at the end of the follow up period of 43 months.<sup>13</sup> The role of EMR for salvage treatment for local recurrence leading to increased disease free survival after definitive chemoradiation has also been reported.<sup>15</sup>

In the current issue of *Clinical and Translational Gastroenterology*, a retrospective single center study in Japan evaluated 66 patients with superficial esophageal squamous cell carcinoma (SESCC) who refused esophagectomy but elected endoscopic resection (ER) plus chemoradiotherapy (CRT). The majority (65%) of the patients had T1b superficial esophageal squamous cell carcinoma and 55% of the tumors had lymphovascular invasion. Endoscopic resection was performed in most cases (82%) with endoscopic submucosal dissection (ESD). After confirmation of post resection ulcer resolution, the predefined standard chemotherapy regimen was given with a radiation dose modified based on vertical margin positivity (boost dose given only if positive margins). Patients were followed up according to protocol with repeat imaging, endoscopy and blood work. The study showed 1, 3 and 5-year overall survival of 98%, 87% and 75% respectively. This was comparable to overall survival after esophagectomy alone and CRT alone in Stage 1 esophageal cancer (EC).<sup>16,17</sup> In a similar prior study that compared combined ER+ CRT vs. CRT alone for early stage SCC, a trend toward higher overall 3 year survival in ER+ CRT group (90% in ER+CRT vs. 63.2% in CRT alone group) was observed.<sup>14</sup> The study reported metastatic recurrence free remission rates of 100, 94 and 92% at 1-,3- and 5 years, respectively, which was similar to a prior study where ESD+ CRT was compared with CRT alone revealing a 94% metastatic free recurrence at 34 months in patients with stage T1b SCC.<sup>14</sup> The same study reported local recurrence of 19% in the CRT alone group (vs. the present study with a local recurrence rate of 3% for ESD combined with CRT).

Esophagectomy is a highly invasive surgery which carries high post-operative morbidity (40–50%) and mortality (2–9.5%) and is not suitable for patients with advanced age

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Received 24 August 2017; accepted 23 October 2017

and/or multiple comorbidities.<sup>18</sup> Esophagectomy has also been shown to impact quality of life (QOL) due to a high rate of postoperative complications such as anastomotic leak and cardiopulmonary events.<sup>13</sup> Chemoradiation alone has been reserved for patients with metastatic disease or in conjunction with esophagectomy in patients with locally advanced disease. Chemoradiation alone is an option but has been shown to have higher side effects<sup>19</sup> and a higher risk of local recurrence,<sup>20</sup> as high as 19–29%.<sup>14</sup> In the present study, combining endoscopic resection with adjuvant dose-reduced chemoradiation, the local recurrence rate was shown to be 3%, which is encouraging. In the present study, 20% of the patients had synchronous extra esophageal cancer and the study enrolled patients > 75 years, factors which could have influenced the overall survival rates in the group receiving endoscopic resection plus adjuvant chemoradiation. Despite these inclusions, the overall survival rates remained comparable to esophagectomy and definitive CRT.

The present study confirmed lymphovascular invasion (LVI) as strongly associated with metastatic recurrence.<sup>21</sup> Lymphovascular invasion has been an indication for surgical resection in esophageal adenocarcinoma. For early esophageal adenocarcinoma, tumor size (> 2 cm), stage, and grade have been shown to be independent predictors of LN involvement.<sup>22</sup> Based on their population of non-operative candidates, patients in the current study were not excluded on the basis of LVI. If the approach described here were to be adopted for potential surgical candidates with SCC, LVI would be an important factor to consider in treatment allocation.

This study has several strengths.<sup>21</sup> It represents larger sample ( $n=66$ ) as well as longer follow-up (51 months) than previously reported ( $n=16$ , follow up to 43 months). The approach of reduced radiation dose highlighted in this study (depending on tumor margins), leading to reduced radiation related side effects is also novel. Endoscopic and imaging surveillance of these patients is critical and they report 100% follow-up for an average of 4 years. It is important to note that the study was single center and retrospective. The results could be particular to their approach or patient population. The outcomes are also harder to interpret definitely without a control group in contrast to other studies comparing endoscopic resection plus CRT to either radical esophagectomy<sup>13</sup> or definitive CRT.<sup>14</sup> In the present study, 82% of patients had ESD for local resection of tumor. ESD is technically demanding and there are many Western medical centers without access to this approach. The present study does not specify the specific size criteria used for ESD vs. EMR which would be of benefit if their approach was adopted more widely. While the study had a larger sample size compared to previous studies ( $n=66$ ), this approach would be strengthened by replication and prospective study.

Overall as now shown by multiple studies<sup>1,7,14</sup> endoscopic treatments are emerging as front line approaches for early esophageal malignancies. The present study highlights the excellent outcomes achieved with endoscopic management for squamous cell tumors as well. This study also highlights a new paradigm where chemotherapy and or radiation therapy are combined with local endoscopic resection. In this paradigm, the local resection is provided by an endoscopic approach which is organ sparing. It is encouraging that for T1b cancers, endoscopic resection with adjuvant chemoradiation

demonstrated equivalent or improved control of disease. In regards to long-term outcomes, current studies report follow up to 4 years for modest numbers of patients. Longer term follow-up with larger sample sizes will be critical to understand if organ sparing approaches have the same long term durability. The Cochrane database study comparing surgical vs. non-surgical treatment (chemoradiation) for esophageal cancer suggested comparable long term survival with better health-related quality of life and shorter hospital stays in the non-surgical treatment arm.<sup>23</sup> If such results continue to be borne out, approaches combining endoscopic resection with adjuvant chemoradiation may be found to offer an appealing mix of good oncologic outcomes, favorable complication profiles, and decreased system costs.

## CONFLICT OF INTEREST

**Guarantor of the article:** Dr. Field F. Willingham, MD, MPH, FASGE.

**Specific author contribution:** Rushikesh Shah, MD: Reviewed initial study. Participated in extensive literature search. Contributed in writing and editing editorial draft. Field F Willingham: Contributed in writing and extensive editing and revisions of editorial draft. Literature review. Expressed opinion based on our center's experience in endoscopic treatment of esophageal cancers.

**Financial support:** None.

**Potential competing interest:** None.

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