



Endoscopic resection with adjuvant chemo-radiotherapy for superficial esophageal squamous cell carcinoma: A critical review

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ABSTRACT

Radical esophagectomy with extended lymph node dissection is considered the standard of care in treatment of squamous cell carcinoma of esophagus with deep mucosal invasion (pT1a m3) or submucosal involvement (pT1b). However, despite the increasing use of minimally invasive approaches, it remains a major surgery associated with significant morbidities and even mortality risk. Endoscopic resection (ER) results in excellent local control in early superficial mucosal (pT1a) disease yet there is substantial risk of lymph node metastases in T1b disease. Therefore, ER followed by combined with chemo-radiotherapy (CRT) would potentially improve the outcome in pT1a m3 or pT1b disease and would be an attractive conservative alternative to esophagectomy. Retrospective series published so far have shown promising results for this combined treatment. Herein the current literature of the indications, treatment outcome and toxicities of this treatment strategy are discussed and critically reviewed.

1. Introduction

With the recent advances in diagnostic modalities, the diagnosis incidence of superficial squamous cell carcinoma of esophagus is increasing. Esophagectomy with extended lymph node dissection has been historically the standard of care in treatment of squamous cell carcinoma of esophagus with deep mucosal or submucosal involvement. However, despite recent surgical progress in minimally invasive techniques (Luketich et al., 2012), it remains a major surgery associated with increased morbidity and even mortality. Patients' quality of life, nutritional status and functional outcome are often jeopardized post-operatively.

Endoscopic mucosal resection (EMR) or submucosal dissection (ESD) are novel and increasingly applied techniques of endoscopic resection (ER) which allow a conservative treatment of superficial esophageal cancer lesions. By en-bloc removal of the tumor, pathological information including the depth of the invasion and the presence of lymphatic or vascular invasion can also be obtained. It is well known that ESD enables removal of larger and deeper lesions down to the submucosal layer, and results in a low local recurrence rate ranging

between 0 and 17% (Sgourakis et al., 2013). The National Comprehensive Cancer Network (NCCN) guidelines suggest that ER should be the preferred treatment option for carcinoma-in-situ, T1a disease of less than 2 cm of diameter and with a well or moderately-differentiated histology (Network NCC, 2017). For the Japanese Esophageal Society guidelines (Kuwano et al., 2015), ESD is indicated for T1a esophageal cancer involving the epithelium or lamina propria with less than two-third of circumference involved. It shows that ER alone is becoming the standard of care in superficial T1a disease.

Although EMR or ESD can achieve good local tumor control rates, there is a considerably risk of subclinical lymph node metastases for disease involving the muscularis mucosa (m3) or the submucosa (sm). Based on the result of JCOG 0502 trial (Akutsu et al., 2016), twenty-seven percent of patients with clinical node negative pT1 disease may harbor pathological positive lymph-nodes. Sgourakis et al. observed a 27%, 36% and 55% risk of lymph-node metastases for sm1, sm2 and sm3 lesions, respectively (Sgourakis et al., 2013). Additional risk factors of lymph-node metastases include grade 3 disease, lymphatic or vascular invasion. In view of the high risk of lymphatic spread, management of subclinical lymph node metastases is crucial for patients

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with submucosal disease, especially with deep submucosal involvement. Radical esophagectomy with extended lymph-node dissection is therefore still the standard of care for pT1b disease, even in the presence of clinical node negative disease.

Definitive chemo-radiotherapy (CRT) is an alternative treatment option for early superficial esophageal cancer (Kodaira et al., 2010). With the merit of organ preservation, definitive CRT has been showing overall survival rates comparable to radical surgery. However, local failure rates up to 30% and morbidities linked to dose escalation represent the major pitfalls of this strategy (Kato et al., 2009).

ER in combination with adjuvant CRT may represent, therefore, an emerging conservative treatment modality for esophageal lesions involving the muscularis mucosa (pT1a m3) or the submucosa (pT1b). While ER can ensure local control and confirm the depth of invasion, adjuvant CRT could consolidate the local control in presence of positive margins or deep lesions and improve progression-free survival rates by treating regional lymph nodes at risk of tumor invasion.

In this review we will summarize and critically discuss the available clinical data exploring the combination of ER with adjuvant CRT as treatment modality for pT1a m3 and early pT1b squamous cell esophageal cancer.

2. Material and methods

In September 2017, a literature search was performed in the PubMed and Web of Science databases. Full-text English language articles reporting on ER with additional CRT for submucosal squamous cell carcinoma of esophagus were identified and reviewed. The final reference list was generated based on the originality and relevance to the broad scope of this review and 5 full text papers articles were identified matching the terms of research and included in this critical review.

3. Results

All available literature is based on retrospective single center series. A total of five studies were analyzed including in total 168 patients, with the largest series including 66 patients (Ikeda et al., 2015; Shimizu et al., 2004; Kawaguchi et al., 2015; Mochizuki et al., 2011; Hamada et al., 2017; Uchinami et al., 2016). These six studies were published between 2004 and August 2017 and were all conducted in Japan. No prospective or randomized trials have been published on this topic. Three studies included a comparative group, represented by patients with similar tumor characteristics treated with radical esophagectomy (Shimizu et al., 2004), definitive CRT or RT alone (Kawaguchi et al., 2015; Uchinami et al., 2016), and ESD plus surgery or ESD alone (Ikeda et al., 2015). Table 1 illustrates the six studies analyzed in this review.

3.1. Baseline characteristics

On the whole study population, the age of the analyzed patients ranged between 42 and 78 years. Most lesions were located in the thoracic esophagus and more than 50% of tumors were located at mid thoracic esophagus. Thirty one patients (18%) were treated with EMR, otherwise with ESD. The median tumor size varied between 24 and 44 mm (range, 14–55 mm). There was much heterogeneity in terms of tumor depth: Shimizu et al., (2004), Mochizuki et al., (2011) and Uchinami et al. (2016) included mainly patients with pT1a m3 or pT1b sm1 disease (Shimizu et al., 2004; Mochizuki et al., 2011; Uchinami et al., 2016), while the other three series included more than half of the patients with a deeper submucosal involvement (pT1b sm2 or deeper). Ikeda et al., (2015) and Hamada et al., (2017) included 73% and 55% of tumors with lympho-vascular invasion (LVI), respectively, a prognostic factor associated with a higher risk of lymph node involvement and distant metastases. In one series no patient presented LVI, while the remaining two studies do not report on that.

3.2. Chemo-radiotherapy regimens

The most common delivered dose of radiotherapy was 40 Gy or 41.4 Gy in 20 or 23 daily fractions of 2 Gy or 1.8 Gy, over a 5 weeks' time period. Ten to 20 Gy of boost were delivered in case of positive margins after ER, suspected lymph node metastases or deep submucosal lesions (sm3). The RT technique was not specified and detailed in all series, but assumed to be based on a three-dimensional conformal RT beam arrangement. For the RT portal there were minor variations among different studies. In general, for cervical or upper thoracic esophageal lesions the RT portal most would include the bilateral supraclavicular fossa down to the bifurcation of trachea or gastro-esophageal junction (GEJ). For mid thoracic lesions the bilateral supraclavicular fossa down to the GEJ was included in the RT field. For lesions involving the lower thoracic esophagus the supraclavicular fossa would be omitted while the lower border was extended to the lesser curvature of the stomach and included the celiac axis lymph-nodes.

The concomitant chemotherapy regimen consisted in most of the series of infusional 5-fluorouracil (5-FU) and cisplatin (CDDP), mostly delivered every 3–4 weeks. Nedaplatin was used instead of CDDP in selected patients with impaired renal function. The most common regimen was 5-FU at 700 mg/m² for 96 h with CDDP at 70 mg/m² every 3–4 weeks. One series used continuous 5-FU infusion with a weekly low-dose CDDP schedule (Mochizuki et al., 2011). Omission of concomitant CDDP was allowed for patients older than 75 years old in one series (Kawaguchi et al., 2015), while a reduced chemotherapy dose (75% of the standard dose) was used in elderly (≥80 years) and frail patients in the Uchinami et al. series (Uchinami et al., 2016).

3.3. Outcomes

Local control was excellent across the different studies with local failure rates ranging from 0% to 9%. Overall there were only 3 patients who recurred locally. One local failure in Ikeda et al., (2015) series was associated with concomitant distant failure and was observed in a patient presenting a sm3 lesion associated with LVI (Ikeda et al., 2015). The other 2 local failures were observed in Hamada et al., (2017) series but the details were not reported (Hamada et al., 2017). There was 14% of metachronous esophageal lesions after ER and adjuvant CRT in Hamada et al., (2017) series but were all successfully treated with salvage ER (Hamada et al., 2017).

The distant failure rate ranged from 0% to 27.2%. Ikeda et al., (2015) reported that there were 3 out of 11 patients (27.2%) recurring in the liver or in lymph-nodes (Ikeda et al., 2015). In these three patients, tumors presented LVI and in two of them positive margins were observed after ESD.

The 3-year overall survival (OS) rates ranged from 87% to 100% in all studies. The 3-year OS rate of 89% observed in the Ikeda et al., (2015) series was probably overestimated as calculated in a group including both patients treated with ESD plus adjuvant CRT (ESD-CRT) and patients treated with ESD followed by radical esophagectomy (Ikeda et al., 2015). Looking at patients treated with ESD with adjuvant CRT, the 3-year relapse-free survival rate was only 69.0%.

3.4. Toxicities

Severe grade 3 or more toxicity observed in the analyzed series consisted mostly of hematological toxicities (0–33%) due to the use of concurrent chemotherapy and ranged between 0% to 41%.

Grade 3 esophageal stenosis was reported in 25% of the patients in the Kawaguchi et al., (2015) series (Kawaguchi et al., 2015). Overall, 6 patients presented grade 5 toxicities – two patients died of radiation pneumonitis (Hamada et al., 2017; Uchinami et al., 2016) and four patients died of myocardial infarction or congestive heart failure (Kawaguchi et al., 2015; Uchinami et al., 2016).

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