Risk-stratified clinical management of superficially invasive ESCC after endoscopic resection: finding the sweet spot

Authors: Marnix Jansen[1,2], Jacques Bergman[3]

Institutions:
[1] Department of Pathology, University College London Hospital NHS Trust, London, United Kingdom
[2] Department of Pathology, UCL Cancer Institute, London, United Kingdom
[3] Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands

Correspondence should be addressed to MJ (m.jansen@ucl.ac.uk) or JB (j.j.bergman@amc.uva.nl)

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In this issue of *Endoscopy* Kazuya Takahashi and colleagues report on the long term outcomes of a risk-stratified management approach for patients with superficially invasive esophageal squamous cell carcinoma (ESCC). The key factor driving management decisions for superficial ESCC after endoscopic resection is depth of tumor invasion, as this is linked with the risk of lymph node metastasis (LNM) in these patients.[1,2] For *in situ* ESCC (stage T1a-M1) and ESCC limited to the lamina propria (T1a-M2) the risk of co-incident LNM is estimated to be less than 5%. This marginal risk is deemed acceptable for endoscopic therapy, given the morbidity and mortality associated with esophageal resection. For lesions invading the muscularis mucosae (T1a-MM) the risk of co-incident LNM has been variously reported as 0%-9%, whilst LNM risk for lesions infiltrating the superficial submucosa (<200µm from the muscularis mucosae, stage T1b-SM1) has been reported to lie between 8% and 16%.[3-5] These superficially invasive ESCC lesions (stage T1a-MM and T1b-SM1) have therefore been considered a 'borderline' indication for endoscopic treatment, where management should be individualized and discussed in a multidisciplinary setting in centers with a tertiary referral service for esophageal cancer.

However, these data on LNM risk for stage T1a-MM and T1b-SM1 ESCC have been derived from retrospective histopathologic analyses of resection specimens, which do not reveal the natural history of conservatively treated superficially invasive ESCC. Indeed, studies have suggested that long-term survival of patients with ESCC lesions infiltrating the muscularis mucosae without further poor prognostic indicators, such as lymphovascular invasion (LVI) or poor tumor differentiation, is excellent (>95% tumor-specific survival).[6,7] Given this, there is now a move towards expanding the eligibility for endoscopic therapy to include ESCC patients with infiltration of the muscularis mucosae and superficial submucosa lacking poor prognostic indicators, so-called low-risk disease.[2,8]

Takahashi and colleagues carried out a retrospective analysis of outcomes of patients treated at their institution between August 2004 to November 2013 for superficially invasive ESCC. From an initial endoscopy database of 694 patients who underwent ESD for ESCC during the study period, the authors retained 108 patients who fit the study's inclusion criteria (i.e. histologically proven ESCC, either stage T1a-MM or T1b-SM1, without clinically documented LNMs at time of ESD). After excluding a mere 6 patients because of loss to follow-up, the authors included 102 patients into the final study cohort. All patients had been uniformly clinically evaluated using CT following endoluminal resection. Patients were offered conservative management with strict endoscopic follow-up and CT every 6 months if the lesion lacked poor prognostic indicators and initial CT did not reveal locoregional LNMs. If metastases

were detected during follow-up, patients were offered salvage surgery and/or (chemo)radiotherapy depending on their clinical performance. The median length of follow-up was close to six years.

Retrospective analysis of this cohort showed that the overall 5-year disease specific survival was 97.5% and the 5-year tumor-free survival was 82.1%. 23 patients in this cohort (22.5%) showed poor prognostic indicators (either LVI or poor tumor differentiation, or both) and of this group 12 patients were offered surgery and/or (chemo-)radiotherapy, whilst 11 patients were not offered additional treatment because of co-morbidities. Only two patients across this cohort died of ESCC, whilst metastases were detected in 12 patients on follow-up. LVI was shown to be a strong independent predictor of the development of metastases on follow-up, although the confidence intervals are wide (hazard ratio 5.42, 95% CI 1.39 - 21.18), suggesting significant heterogeneity. Indeed, six of 12 patients that developed metastases were initially assessed as low-risk.

The authors then carried out a subgroup analysis to investigate the combination of patient risk stratification and further treatment on outcome. In this analysis three groups of patients were compared: patients with either T1a-MM or T1b-SM1 disease without any poor prognostic indicators (low risk group); patients with poor prognostic indicators who underwent surgery and/or (chemo-)radiotherapy (high risk-surgery group); and those with poor prognostic indicators who did not undergo additional treatment (high risk-conservative management group). Analysis of survival and tumour recurrence rates showed that tumor-free survival was significantly poorer in high-risk patients who did not undergo additional therapy compared to low risk patients. Vice versa, tumour recurrence was comparable between low-risk patients and high-risk patients who underwent additional therapy following ESD.

So on balance what are the main take-aways from this retrospective data analysis? The data clearly signal that patients with invasion into, but not beyond, the muscularis mucosae and without further poor prognostic indicators such as LVI or poor differentiation likely have a low risk of loco-regional LNMs, suggesting that conservative endoscopic follow-up is a safe and efficacious management option for these patients. Future prospective studies will need to support or refute this contention. Vice versa there is a suggestion that patients with poor prognostic indicators (regardless of invasion depth) who undergo surgery decrease their risk of disease recurrence, however the numbers are small and this again needs stringent verification in larger studies. The natural history of patients with lesions that invade into the superficial submucosa (T1b-SM1) that lack poor histopathologic indicators is less clear. All told there were 13 patients in this study who occupied this middle ground. The authors suggest that in this cohort there is no principal difference between groups stratified for invasion depth. However, there is a trend towards more frequent LVI in patients with T1b-SM1 tumors, suggesting that a diligent histopathologic search for signs of LVI, possibly aided by D2-40 immunohistochemistry to highlight lymphatic vessels, is indicated in these patients. Management decisions for these patients will have to be made on an individualized basis also taking into account co-morbidities and patients' expectations. In this regard the survival data are re-assuring and suggest that again many of these patients will fare well.

This report by Takahashi provides strong support for the safety of an expanded indication for conservative management of superficially invasive ESCC after endoluminal resection. Future prospective studies are essential to define which high risk features in these cancers predict the need for additional treatment. This will narrow down this category of patients that require additional aggressive management after local endoluminal excision further.

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