

# The renaissance of photodynamic therapy for early esophageal cancer: is it the time?

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Early esophageal cancer is a superficial tumor limited to the mucosal layers of the esophagus. In the last decade, the increased use of endoscopic surveillance in asymptomatic patients has contributed to an increased proportion of patients with early esophageal cancer (1). Historically, radical esophagectomy is considered the standard treatment for early esophageal cancer. However, it is a complex procedure, associated with a mortality of 6–10% and morbidity of 43–56% (2). Thus, young asymptomatic patients may be reluctant to accept esophagectomy and others (i.e., elderly patients with concomitant comorbidities) may be unfit for this treatment. The prognosis for patients treated for superficial esophageal cancer is significantly better than that of patients with advanced esophageal cancer, even those found in other relatively early-stage disease (3,4). Thus, in the last decade there has been a growing tendency to search conservative local treatments with curative intent for early esophageal cancer. Among these, endoscopic treatments as photodynamic therapy (PDT) and endoscopic submucosal dissection (ESD) have shown potential for providing effective cancer treatment with much less treatment-related morbidity. Berry *et al.* (2) using the data from the Surveillance, Epidemiology, and End Results (SEER) data base evaluated 1,458 patients with early esophageal cancer (T1N0M0) undergoing esophagectomy (n=1,204; 83%) and endoscopic treatment only (n=254; 17%). No significant difference was found between two study groups regarding 5-year overall survival (OS) (P=0.07) and 5-year cancer specific survival (CSS) (P=0.10). After propensity-score

analysis, endoscopic group presented a better CSS than surgery group (P=0.003), indicating higher changes of dying from other causes. Japanese Esophageal Society approved ESD as curative treatment for intramucosal cancer involving the epithelium and *lamina propria* occupying less than 2/3 of the lumen of the esophagus (5). National Institute for Health and Clinical Excellence (NICE) recommendations (6) reported that the safety of PDT for early-stage esophageal cancer appeared adequate. Among the different analyzed series, complete response was achieved from 37% to 100% of cases. For stage T1a tumors the response rate was 67% while for *in situ* carcinoma was 91%.

From a technical point of view, the main difference between ESD and PDT is that the first is a resective procedure while the second is a conservative procedure. Standard ESD allows the resection of superficial esophageal cancer in a stepwise manner including marker the lesion, incision and submucosal dissection with simultaneous hemostasis (7). Thus, it requires advanced skills and is associated with a substantial risk of major complications including bleeding, mediastinitis, and perforations. Conversely, PDT involves administration of photosensitizing agent followed by the application of a specific wavelength of light, leading to intracellular photo excitation and injury. Being an ablative treatment, it preserves the integrity of the esophagus and in theory reduces the risk of major complications. Despite PDT is technically easy, well-tolerated by patients and associated with low morbidity, over the years it has lost popularity in

favor of PDT, that is currently considered the treatment of choice for superficial esophageal cancer. Recently, the advantages of PDT are being reconsidered after favorable results of salvage treatment in patients with local failure after CRT.

In line with this tendency, Hua *et al.* (8) conducted a retrospective study to demonstrate the efficacy and safety of PDT over ESD as curative treatment for early esophageal cancer, an issue not been reported before. Patients were scheduled for endoscopic treatment based on standard and modern diagnostic examinations including electronic gastroscopy, endoscopic ultrasonography (EUS), and PET-CT scan that allowed to define the length and depth of esophageal wall invasion, the presence of lymph node involvement and of distant metastasis. In line with the recommendations of Japanese Esophageal Society (5), only patients with superficial esophageal cancer underwent ESD or PDT treatment while patients with tumor depth invasion beyond the mucosal layer, or with involvement of lymph node or with distant metastasis were excluded. Sixty-six patients were included in the final analysis. Of these, 30 were treated with PDT and the other 36 with ESD. The two study groups were well matched regarding clinical symptoms ( $P=0.198$ ), histology ( $P=0.464$ ), circumferential extension of the tumor ( $P=0.496$ ), and tumor invasion depth ( $P=0.952$ ). Kaplan-Meier analysis showed no significant difference between two study groups regarding DFS ( $P=0.193$ ). ESD compared to PDT presented higher bleeding (33% *vs.* 6%,  $P=0.008$ ) and perforation rate (16% *vs.* 0%,  $P=0.019$ ) while PDT had higher stricture rate (50% *vs.* 16.7%,  $P=0.004$ ) and procedural cost ( $P=0.01$ ) than PDT. Despite all, the length of hospital stay was similar two groups ( $P=0.549$ ).

These results should be critically analyzed before drawing definitive conclusions on the renaissance of PDT for management of superficial esophageal tumor. First, the allocation of patients in PDT or in ESD group was based on the surgeon's preference, and no additional statistical adjustments (i.e., propensity-matched analysis) were performed to limit the bias of the retrospective patient selection. Second, the authors did not evaluate OS and CSS, thus it is challenging to demonstrate a real survival benefit of the two endoscopic procedures. Major complications occurred after ESD and PDT, but the paper was lacking of data on their treatments and outcome. In theory, patients could die during the follow-up for the complications related to the procedure rather than for cancer. A recent review (9) reported 2.6–10% perforation rate and 0.7–5.2% bleeding

rate after ESD. Most perforations were identified during the procedure and closed with clip. Delayed perforation rarely occurred but they were associated with life threatening conditions as mediastinitis. In line with these data, bleeding and perforation were the main complications after ESD also in the Hua's series (8), but no information regarding the time of diagnosis (intra-procedural or delayed), the treatment (endoscopic closure or surgery) and the outcome were provided by the authors. On the other hand, esophageal stricture is a major complication related to PDT with an incidence ranged from 7% to 35% (10). It can evoke severe dysphagia, and results in a decrease in quality of life or, occasionally, aspiration pneumonia. Despite in the series of Hua *et al.* (8), 50% of patients undergoing PDT presented stricture, no information on the grade of stricture, time of diagnosis, the treatment performed (i.e., endoscopic balloon dilation, local and systemic injection of steroids, or insertion of temporal esophageal stent), and the outcome were provided by the authors. Additionally, it could be interesting to identify risk factors for stricture after PDT (i.e., circumferential extension of the tumor, tumor invasion depth, number of PDT procedure) in order to perform preventive treatments (i.e., dilation) and more frequent endoscopic follow-up in high risk patients.

In conclusion, the authors should be commended for their work. They showed that among different ETs, PDT is a safe and promising local curative treatment option for early gastric cancer. Despite simpler and safer than ESD, however PDT it is not lacking of complications. Esophageal stricture is an important concern to be aware of in the post-operative review of patients undergoing PDT. In the future, the effect of PDT could be improved with a combined treatment with chemotherapy (10) or using new generation of photosensitizing agent (11).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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