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Long-Term Follow-up for Patients with Early Esophageal Cancer Treated with Photodynamic Therapy (PDT)

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Running heads: Photodynamic therapy for esophageal cancer.

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Photodynamic therapy (PDT) has been used for the endoscopic therapy of early esophageal cancer. However, its long-term survival outcome remains unknown in literature.

Patients and method:

We analyzed the long-term survival outcomes of patients with early esophageal cancer (clinical stage I) treated with Photofrin-based photodynamic therapy (PDT) compared with esophagectomy performed by a single surgeon.

Results:

There were 15 and 16 patients undergoing PDT and esophagectomy enrolled in the current study, respectively. Complete response was achieved in ten of 15 patients (66.7%) after PDT, thirteen patients (86%) after adjuvant chemoradiation (CCRT). There was no mortality was observed after PDT. However, severe complications occurred in 3 patients, including trachea-esophageal fistulae, esophageal stenosis and skin photosensitivity. With the median follow-up time for patients after PDT of 110.2 months (±9.6 months), 4 patients experienced local recurrence and 3 patients developed recurrence in the regional lymph node, yielding a successful local control rate of 73.3% for the primary tumor. There were 7 (46.7%) patients who died during clinical follow-up of this cohort, 5 (33.3%) from disease progression of esophageal cancer and 2 from other diseases. The five-year survival rate after PDT was 64.3%, compared to 70.9% of the patients after esophagectomy, no significant difference was found between the two study groups.(P=0.72)

Conclusion:

Our preliminary results suggested that PDT might provide an equivalent long-term oncological outcome as compared to that done by esophagectomy for early esophageal cancer. A prospective randomized clinical trial comparing the results of esophagectomy and other endoscopic abrasive therapies is warranted in the future.

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Esophageal cancer is still a disease threatening the health of human worldwide with increasing incidence across the world in these two decades[1,2]. Surgery alone or in combination with neoadjuvant chemoradiation remains the treatment of choice for the patients with resectable disease[3]. Perioperative morbidity and mortality remains a concern for a substantial portion of patients after esophagectomy even in the hands of experienced surgeons[4,5]. The introduction of minimally invasive esophagectomy has become popular in treating esophageal cancer which provide a similar oncological outcome whereas a lower risk of preoperative morbidity[6,7]. On the other hand, for the lesion confined within the mucosa without evidence of lymph node or distant metastasis, local abrasion therapies through endoscopy have been demonstrated the potential effectiveness for removal of the lesions and provide the long term survival benefit[8,9]. Various options , including endoscopic submucosal dissection[16], radio-frequency abrasion[10] or photodynamic therapy[11], have been adopted to treat patients with early esophageal cancer in this minimally invasive endoscopic setting. Photodynamic therapy involves the intravenous, oral or local administration of a photosensitizer, which specifically retains in the tumor and leads to tumor-specific cytotoxic effect after irradiation with a certain wavelength of light. The PDT has been applied to treat patients with early esophageal cancer with complete response rate ranging from 64% to 80%[12-16]. After repeated application, the response rate can be raised up to 100%[17]. However, the long-term survival results of PDT in treating early esophageal cancer is lacking in literature. In current study, we evaluated the long-term results of early esophageal cancer patients after photodynamic therapy.

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Patients and Methods

During 2002 to 2013, thirty-one patients of early esophageal cancer was treated by a single surgeon, among whom, 16 undergoing esophagectomy with thoracic and abdominal lymph node dissection; whereas 15 undergoing endoscopic PDT due to refusal of surgery by the patients (n=4) or unsuitable for surgery due to high surgical risk (n=11). (During 2002 to 2013, thirty-one patients with early esophageal cancer were treated by a single surgeon; 16 underwent esophagectomy with thoracic and abdominal lymph node dissection, and 15 underwent endoscopic PDT due to patient's refusal of surgery (n=4) and high-risk surgical profile (n=11).)The preoperative evaluation included computed tomography, endoscopic ultrasound and position emission tomography. No regional lymph node metastasis or distant metastasis was detected by the staging studies before applying PDT to the patients. The indication of PDT was T1N0M0 disease by the staging studies. Adjuvant chemoradiation are given to patients with T1b disease or residual disease after PDT, and we have adopted endoscopic submucosal dissection for this patient group since 2013. Since 2013, we start to adopted endoscopic submucosal dissection for such status of disease. The study cohort was therefore collected from 2002 to 2013. Informed consent was obtained from all patients prior to their enrollment of study. The study was approved by the Institution Review Board (IRB) of the hospital before initiating PDT treatment for each patient (IRB/REC NTUH No.: 940610).

Photodynamic therapy

Photofrin (Ascan Pharma, Mt-St-Hilaire, Canada) of 2mg/kg was given intravenously, followed by light illumination with 630 nm wavelength 48 hours later. The light was introduced with flexible cylindrical probe mounted on 400 um quartz fiber with an active length of 2-to5 cm in the tip. Light was generated from a diode laser system (CAM, UCL). The energy was given with the dosage of 300 J/cm under the power

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of 400 mW/cm applied in 750 sec. The lesion was re-checked within one week after injection of Photofrin. An additional 100 J/cm would be given once an unsatisfactory response of the tumor was detected under secondary inspection. Because the use of PDT must be approved by the IRB in our country, which typically takes about three to four weeks before the procedure, APC (argon plasma coagulation) was given 2 to 3 weeks before PDT in 4 cases of patients during the waiting period for IRB approval.

Post-treatment care and clinical follow-up

The patients resumed oral intake on the day after photodynamic therapy. Proton pump inhibitor and Sucrate Gel were prescribed for one month after treatment. Endoscopic evaluation was given every three months in the first two years after PDT and every 6 months after 2 years post-PDT. Computed tomography was given in every 3 to 6 months after treatment.

Statistical analysis

All continuous values were presented as mean ± standard deviation (SD). The demographic and clinical data between different surgical groups were compared with the c^2 test or Fisher exact test, as appropriate. The duration of survival was analyzed by Kaplan-Meier method. All the factors significant for influencing the survival results were further examined by Cox-regression model. All analysis was performed by SPSS software (SPSS Inc, Chicago, IL).

Results

The clinical characteristics are listed in Table 1. There were 12 patients with stage I esophageal cancer with complete response of the tumor after PDT (75%). Adjuvant CCRT was given for 4 patients because of residual disease, one of whom had persistent disease after CCRT who received esophagectomy afterward. Prior to PDT,

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IRB review and approval for each patient in Taiwan could take about 3 to 4 weeks. We used endoscopic APC abrasion for each of these 4 patients before PDT. Complications were noted in 3 patients, including photosensitivity (1), stricture (1) and TE fistulae (1). Of the patients that developed TEF, one had double cancers and had received chemotherapy for leukemia with complete response before PDT. Double stent was given for the patient before discharge after PDT treatment.

The clinical profiles of the patients treated with PDT and esophagectomy are postulated in Table 1. The Kapla Miere survival curve was demonstrated in the figure 1. The mean 5 year-survival of PDT and esophagectomy groups were 64.3 % and 70.9 % respectively. There was no significant difference in survival between patients undergoing PDT and esophagectomy(p=0.72). The characteristics of patients receiving PDT are listed in Table 2. There were 4 patients who had local recurrence with a successful control rate of 73 % for the primary tumor during follow-up period. Three patients developed regional lymph node recurrence. Of the **7** patients with recurrence, 5 died from cancer progression. The remaining two who received esophagectomy**,** one died from adhesion ileus 6 months after surgery and the other has remained living well in recent follow-up. Six patients suffered from head and neck cancer after esophageal cancer treatment, one of whom died from disease progression of head and neck cancer.

Discussion

Endoscopic abrasive therapy has gradually been accepted as an effective treatment option**,** in addition to esophagectomy**,** in caring patients with early esophageal cancer. However, little is known about the long-term results after the initial therapy, especially the outcome after PDT for early esophageal cancer. This is the first study in literature to demonstrate the comparative results in PDT and esophagectomy for

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early esophageal cancer. The selection of PDT in our study was reserved for those who were unsuitable or unwilling to undergo surgery. Of the five patients who died from disease progression, one resulted from adhesion ileus and the other from secondary malignancy. The 5-year overall survival rate was 64.6 %, which is comparable to that of patients after esophagectomy.

There were patients with severe complications, including TEF and stricture of the esophagus in one patient. The stricture was relieved after several times of esophageal dilatation. It has been reported that the presence of these severe complications was more frequent in those patients with previous history of chemo/radiation. The tissue might be more fragile and less effective of the adjacent tissue to expel the photosensitizer, thus more vulnerable to severe complications. A reduced dosage is suggested for these patients at high risk of treatment related complications during light irradiation.

Endoscopic regular follow-up of the lesion is performed for all of the patients. Once residual disease was found in the tumor bed, adjuvant CCRT would be given for these patients. Of these patients after PDT, the complete response rate was 66.7 % (10/15). With the aid of adjuvant CCRT, the complete response rate could be achieved in 86 % (13/15) of the patients. Later in the cohort study period, neoadjuvant APC was given during the waiting period for our IRB approval, which might have helped in increasing the response rate of PDT. However, the risk of complications might also have been increased with such intervention. Fortunately, all of these patients had an uneventful course and complete response to PDT. Of the 5 patients who died from disease progression in our study, two had recurrence in the primary tumor site and three had recurrence in the regional lymph node. It is worth noting that five of our patients (n=5, 33.3%) suffered from secondary cancer of head and neck, which led to one death. Maekawa et al found that 30 % of the patients developed

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secondary cancer after endoscopic resection for esophageal cancer[18]. Similar results were found in esophageal cancer patients with a high incidence of secondary cancer (14%) after definitive chemoradiation[19] **,** among whom the head and neck cancer accounts for the most frequent malignancy detected [18,19]. The risk of secondary cancer can be increased with time of survival after PDT[19]. Our preliminary experience demonstrates the importance of regular follow-up of the systemic condition, even with successful control of the primary tumor for every esophageal cancer patient after PDT.

As treatment options for earl distinct intervention plans and thus may be applied to different situations during early disease. The ESD is suitable for single and small lesion[20]. The FRA is more frequently applied to Barrett's esophagus-associated dysplasia[21] . PDT has deeper penetration and thus can be used to treat tumor with deep-seated invasion. With recurrence after definitive CCRT, PDT has been used as the salvage treatment for patients of esophageal cancer with 91% and 50% of one-year survival rate for those who with or without complete response of esophageal cancer after PDT respectively[22]. The current report is the first study in literature to demonstrate that the long-term survival outcome of PDT in treating early esophageal cancer is comparable to those of esophagectomy**.** Therefore, the difference between PDT and other endoscopic therapeutic options is worth further investigation.

A major limitation of this study is the small study population. Selection bias and heterogeneity in patient characteristics cannot be avoided in the analysis. PDT was used for patients with high risk profiles for surgical complications or unwilling to undergo surgery. Although the survival results between the surgical and PDT group has no statistical difference in the current study, further research of a larger population-based study will be needed. Surgical resection remains the gold standard for lesions with the suspicion of lymph node metastasis or persistent disease after

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PDT or other non-surgical treatment profiles. Only surgery is most effective at tumor eradication and accurate in diagnosis of lymph node metastasis. Among the 5 patients who died from disease progression, three suffered from regional lymph node metastasis after PDT, despite no local recurrence in the esophagus. In addition to regular endoscopic survey of the esophagus, regular computed tomography follow-up is also needed after PDT to detect occult lymph node metastasis and allow earlier intervention of other treatment modalities.

Conclusion

PDT is an effective treatment option for early esophageal cancer with acceptable treatment adverse effects and the long-term survival outcome is comparable to that of patients treated with esophagectomy. Yet, a larger population-based study and prospective randomized trial are warranted in future research.

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