Stereotactic radiotherapy in the role of treating local recurrences of esophageal cancers

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Abstract: **Purpose**: To evaluate the stereotactic radiotherapy in the cases of local recurrences of esophageal cancer. **Methods**: Stereotactic body radiotherapy (SBRT) is a rapidly expanding novel technique combining a short treatment time together with high local efficacy and an acceptable toxicity profile. In this study, 6 patients recurrent esophageal cancer in the neck lymph nodes were treated by SBRT in the Department of Oncology, Tri-Service General Hospital (Taiwan). The treatment dose was mean 35.5 Gy in 5 daily fractions, with a prescribed dose to 65 and 82% isodose, for each patient respectively, utilizing a volumetric arc therapy technique, a 6-MV photon beam and an Elekta Synergy linear accelerator. The maximum dose in the patients was mean 46 Gy. The maximum doses for the surrounding major blood vessels were between 34.8 and 46.8 Gy. Maximum doses to the trachea and the esophagus in the first patient were mean 30.2 Gy. **Results**: The treatment was delivered without any unintentional treatment interruptions and any treatment-related toxicity. The intrafractional movements, during all fractions of radiotherapy were under 3 mm, indicating that 3-point thermoplastic mask during SBRT in the neck region. All the patients tolerated the treatment well and did not experience any significant treatment-related toxicity during the follow-up. **Conclusion**: SBRT utilizing linear accelerators should be considered in patients with localized recurrent esophageal cancer which may benefit for the patients minimal treatment toxicity.
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Introduction

Esophageal cancer is quite rare in comparison to other epithelium tumors. For example, only 1% of cancers originate from the esophagus through the United States and Canada. Although this disease may be rare in comparison to other cancers, the tumors are extremely severe and the cell type of adenocarcinoma are particularly refractive to treatment resulting in a very poor prognosis. For example, 90% of esophageal cancer cases will result in death among US and Canadian adults. Such poor outcomes are mainly attributed to the disease being detected at advanced stages where curative therapy are no longer an option but lack of effective treatment protocols even in early stage is also approach problem. For example, surgery is very difficult for the dangerous and complicated anatomic position. Therefore, esophageal cancer consists of tumors with a generally poor prognosis, and treatment options for patients with disease recurrence are extremely limited.

For over a century, surgical resection was the key modality for the treatment of esophageal cancer. Furthermore, surgical resection also remains a central treatment modality for patients with localized esophageal cancer and provides potentially curative treatment. Besides from surgery, Chemo-radiotherapy (CRT) is also another choice because it may induce dramatic changes in tumor. Most of the authors proposed that locally advanced esophageal cancer is an aggressive malignancy with a high recurrence rate〔1〕. Moreover, meta-analyses of chemo-radiation trials suggest that there is a survival benefit for patients receiving neoadjuvant chemo-radiation (nCRT) and surgery compared to patients undergoing surgery alone〔2,3〕. However, the tumors of esophageal tend to be very radio-resistant meaning the using of radiotherapy even for mass reduction is limited〔4〕. Moreover, it is ever reported that the patients with locally advanced esophageal cancer who are treated with trimodality therapy also have a high recurrence rate〔5〕.

Due to the poor patients' prognosis, the possible treatment toxicity should be carefully balanced against its potential benefit and patient quality of life. According to a large study, Koshy et al. reveal that the patients with esophageal cancer, regardless of histology (squamous cell carcinoma or adenocarcinoma), all have a poor prognosis, with a reported mean 3-year overall survival rate of between

40 and 50%〔6〕. Despite recent advances in radiation treatments and the field of medical oncology during recent decades, the therapy of esophageal cancer has not changed significantly, and the results remain disappointing for the human. The use of neoadjuvant chemo-radiotherapy has been introduced as of 1995. Evidence indicates the nCRT significantly improves survival in patients with locally advanced esophageal compared with surgery alone〔9,21〕. Major histopathological response – defined as absence or < 10% vital residual tumor cells (VRTC) in the resected esophagus without nodal involvement – is a common used criterion for defining a favorable response to nCRT〔22,23〕. The Radiation Therapy Oncology Group (RTOG) 85-01 trial demonstrated that patients treated with chemo-radiation have a significantly better outcome compared with patients treated with radiotherapy alone〔7〕. In the meanwhile, the Intergroup 0123 (RTOG 9405) trial provided evidence that dose escalation (increasing the dose from 50.4 to 64.8 Gy) has no benefit in victims with esophageal cancers〔8〕. The reasons for the negative findings remain un-clear, however, the treatment-related toxicity (specifically lung toxicity) of the higher dose may be the cause of the inferior prognosis of patients randomized in the arm with a higher radiation dose.

Moreover, the CROSS (chemo-radiotherapy for esophageal cancer followed by surgical study) trial has become the most influential study in the management of locally advanced esophageal cancer, due to the unprecedented survival outcome with acceptable toxicity for patients enrolled in the multimodality management arm of the trial. The CROSS study showed benefit of even lower doses of radiation using 41.4 Gy in 23 fractions, administered with weekly carboplatin and paclitaxel chemotherapy〔9〕. There are several notable findings from CROSS that will influence radiation oncology management and serve as important benchmarks. The radiation dose delivered, 41.4Gy in 23 fractions, is lower than traditional doses of 45 to 50 Gy or higher. In the setting, of concurrent carboplatin/taxol chemo-therapy, it has been suggested that radiation doses necessary to satirize microscopic disease. The reduced dose may potentially reduce the risk associated with subsequent surgical resection. Besides, it showed a remarkable median overall survival of 49.4 months for patients who received neoadjuvant chemo-radiation followed by surgical resection versus 24.0 months for those patients who received surgical alone. As a complete response is obtained in only ~30% of patients treated with concomitant chemo-radiation, subsequent esophagectomy appears to be necessary for the patients〔10〕. However, Tepper and his co-workers found that surgery alone has conferred a worse outcome compared with tri-modality treatment〔11〕. Patient selection for this treatment should perform with care, particularly with regard to patient nutrition and performance status. Tri-modality treatment, i.e., neoadjuvant chemoradiation followed by surgery, represents the current standard of care for patients with localized esophageal cancer. However, this treatment is associated with significant morbidity〔12〕.

Furthermore, there are no clear recommendations regarding the frequency and imaging techniques to be used during the follow-up of esophageal cancer patients following radical therapy. In clinic, we could do is that to monitor tri-monthly upper gastrointestinal endoscopy together with computed tomography, to total omission of the follow-up, to refer the patients to a general practitioner and to wait for clinically manifested disease relapse. Moreover, there is no evidence of any benefit of using imaging modalities, endoscopy or serum tumor markers for the follow-up of patients with recurrence. In fact, there is only limited evidence that salvage treatment prolong patient survival〔12〕. The majority of esophageal cancer patients following radical therapy will eventually experience disease relapse. Several treatment options are available for these patients. In the case of local relapse in the esophagus, surgery represents a potentially curative approach. Intraluminal brachytherapy and chemotherapy are only palliative effect〔13〕. If the tumor relapse occurs outside the esophagus in the form of only limited oligometastatic disease, such as only occur in the lymph nodes, surgery or palliative chemotherapy could again be considered. However, quality of life in patients with esophagus cancer is extremely important and platinum-based chemotherapy (cisplatin or carboplatin) poses a significant risk of toxicity.

Radiotherapy as a part of multidisciplinary oncologic care which uses the conventional fractionation is frequently not feasible due to the dose constraints after the primary neoadjuvant chemo-radiation〔14,15〕. The prime goal of radio-therapy is to minimize not only treatment toxicities, but also postoperative complications and hospitals〔38,39,〕. Subsequent to further progression or in patients with metastatic diseases when local therapy is not possible, palliative chemotherapy based on cisplatin, carboplatin, 5-fluorouracil or paclitaxel is another option〔16〕. Now the use of stereotactic body radiotherapy (SBRT) is rapidly expanding in the treatment of almost all tumor types and anatomical regions. SBRT utilizes a high-dose gradient drop off, a limited number of fractions and a high dose per fraction, with a biological equivalent dose usually exceeding 100 Gy. Besides, SBRT has the advantage

of a high probability of local tumor control and, in the meanwhile, a short treatment duration and limited toxicity, leaving the palliative chemotherapy as an option for a subsequent line of treatment following disease progression.

The present study concerns the usage of SBRY in patients with recurrence of esophageal cancer and aims to demonstrate the favorable safety and efficacy of the technique. However, data for the use of SBRT in local recurrence of malignant cells is currently missing〔17,18〕. There are no publications data regarding the usage of SBRT is concerned by many doctors in the world. Therefore, we will analyze the results in this study.

Patients and methods

All the study was performed at Tri-Service General Hospital (Taipei, Taiwan, ROC) since last year and the experiments were all conducted in accordance with the Declaration of Helsinki with ethical approval for this study obtained from Institute Review Board (IRB) of Kaohsiung Armed Forced General Hospital (Kaohsiung City, Taiwan, ROC). In this study, all 6 patients (3 male patients and 3 female patients) diagnosed with esophagus cancer with local recurrence in Department of Medicine, Tri-Service General Hospital were enrolled in our study. The mean age was 65.8 ± 5.4 years.

Tumor volumes. For the purpose of contouring and treatment planning, CT with a 3-mm slide thickness were obtained from the 6 patients. Involved lymph nodes were contoured as the gross tumor volume (GTV) which is the prognostic factor for definitive radiotherapy〔38〕. The clinical target volume (CTV) was identical to the GTV, assuming no extranodal extension of the disease. The planning target volume (CTV) was created by adding a 3-mm margin to the CTV for possible intrafractional movements. The PTV margin was based on institutional SBRT standards. A 3-point thermoplastic mask was utilized for patient immobilization. Organs at risk (OAR; trachea, major vessels and spinal cord) in the vicinity of the PTV were contoured at least 1 cm above and below the PTV. The treatment plan was prepared utilizing the Monaco® planning system by the Monte Carlo Calculation algorithm.

Plan evaluation. In these 6 victims, the local recurrence was outside the high-dose region of previous radiotherapy (refining the high dose as a region with a dose >30 Gy). For the treatment Elekta Synergy linear accelerators were employed (6-MV photon beam, volumetric are therapy technique), the treatment dose was mean 35.5 Gy in 5 daily fractions, for each patient respectively. Since no recommendations or any publications exist regarding the dose for use in the lymph node recurrence of esophageal carcinoma, a dose was selected with respect to the dose constraints of surrounding OARs. The dose gradient as a ratio of the volume of a 100 and 50% isodose was assessed (Paddick)〔18〕, as well as the conformity index (ICRU 83)〔19〕, defined as a ratio of the volume of the PTV that received the prescribed dose as recommended in ICRU 83. To confirm appropriate patient immobilization and setup, three cone beam CT were utilized, two prior to and one subsequent to dose delivery.

Results

A total of 6 patients with esophageal adenocaricinoma (3 cases) and squamous cell carcinoma (3 cases), respectively, who were initially treated with concurrent chemoradiation (50 Gy in 25 fractions, along with 3 cycles of cisplatin and 5-fluorouracil chemotherapy), followed by esophagectomy in the 1st, 3rd, and 5th cases and only observation in the 2nd,4 th, and 6th patients were enrolled in this study. (Table 1)

Surgery was not completed for the 2nd,4th, and 6th patient due to co-morbidities and a complete response after the neoadjuvant treatment, as confirmed by position emission tomography combined with CT (PET/CT). Nodal recurrence in the form of isolated nodal disease with no evidence of other metastases was diagnosed using PET/CT usually. However, PET/CT is not able to distinguish between the tumor and inflammation, particularly in the case of lymph nodes are frequent findings, and as the lymph nodes in the patients could not be biopsied by fine-needle aspiration biopsy, a decision was made to perform 3-deoxy-3-[18F]-fluorothymidine PET (FLR-PET). This technique was used to aid the differential diagnosis, as it exhibits a significantly higher positive predictive value for the diagnosis of neoplasia compared with PET/CT. FLT-PET showed uptake in the same lymph nodes, confirming the high suspicion for the presence of metastatic disease. Each patient was discussed during the multidisciplinary team meetings. Due to the significant risk of surgery in each case, it was decided to proceed with SBRT. These conclusions were discussed with the patients and the rationale, practical aspects and potential side effects of radiotherapy were explained to them. Written informed consent for SBRT and publication of the present study was obtained from the two patients.

In total, 2 patients, 1 man and 1 woman aged 62 and 57 years, respectively, were treated at University Hospital Olomouc. Each patient completed the treatment with SBRT at the beginning of 2016. For disease staging purposes, the TNM 7th classification was utilized 〔20〕.

Table 1. The patients receiving SBRT

Characteristic	1	2	3	4	5	6
Age at Dx. (years old)	58	62	60	72	68	66
Histology	SCC	Adeno	Adeno	SCC	SCC	SCC
Primary Tx	C/T+R/T followed by op	C/T+R/T	C/T+R/T followed by op	C/T+R/T	C/T+R/T followed by op	C/T+R/T
Site of recurrence	Low neck LNs	Neck LNs	Neck LNs	Neck NLs	Low neck LNs	Low neck NN
Number of fractions of SBRT	5	5	5	5	5	5
Dose Prescribed (Gy)	30	40	30	30	40	40
Prescription isodose %	65%	81%	68%	72%	70%	75%
Maxi mum dose (Gy)	45.9	49.2	48.4	46.5	47.5	47.8
Dose gradient (Paddick)	0.17	0.12	0.13	0.14	0.15	0.15
Conformity index (ICRU 83)	0.91	0.88	0.90	0.90	0.83	0.85
Maximum dose to trachea (Gy)	32.6	No.	33.5	34.5	31.5	32.5
Maximum dose to major blood vessels (Gy)	35.4	45.7	40.2	41.3	43.5	45.2
Maximum dose to esophagus (Gy)	27	No	28	32	26	27

SBRT (Stereotactic body radiotherapy), ICUR (International Commission on a Radiation Units)

The patient characteristics are summarized in Table I. The isodose distribution for the treatment plans are shown between 81% and 65% isodoses together with contours for the OAR (organ at risk; trachea, major vessels, and spinal cord). Due to the location of the recurrences, the doses to the trachea, major vessels and esophagus had to be assessed in the first patient, while only the dose to the major blood vessels had to be evaluated in the second patient. The maximum doses to the trachea, the esophagus and the major vessels in the 6 patients varied, and the maximal dose to the major blood vessels was 45.7 Gy in the 2rd patient. The doses to the spinal cord, brachial plexus and lungs were not significant for either patient. The dose to the thyroid gland was not specifically evaluated. The maximum dose was 45.9Gy, 49.2Gy, 48.4Gy, 46.5Gy, 47.5Gy, and 47.8Gy, in patient 1, 2,3,4,5, and 6, respectively. The treatment dose was delivered without any unintentional treatment interruptions and the intrafractional movements during all fractions of radiotherapy were below 3 mm, indicating that a 3-point thermoplastic mask is appropriate for patient immobilization during SBRT in the neck region. Te patients tolerated the treatment well and did not experience any significant treatment-related toxicity during the follow-up.

Discussion

Esophageal cancer is a highly malignant neoplasm and generally carriers a poor prognosis〔24〕. Despite significant advances in surgical and anesthetic technique advances in surgical and anesthetic technique, numerous patients continue to develop recurrences even after an apparently curative resection. The treatment options for patients with recurrent esophageal cancer are only limited and the prognosis is relative poor, with expected survival restricted to months rather than years〔25〕. Evidence of any convincing activity for a given therapeutic approach to support the selection of an optimal treatment modality is mostly missing. Patient performance status, co-morbidities and the patient's own preference should be considered〔26,27〕. In general, there are two treatment options in a case of localized relapse, consisting of either surgical removal of the tumor recurrence, which is often not feasible due to previous radiotherapy and surgery, or systemic palliative chemotherapy〔28,29〕. Surgeons are frequently reluctant to attempt a surgical resection in patients with recurrent esophagus carcinoma due to poor prognosis. Moreover, chemotherapy with the combination of cisplatin and 5-fluorouracil has a limited and very little effect on the survival of esophageal carcinoma, and hence, the addition of taxanes, such as paclitaxel, had been shown to not significantly affect the outcome of the progression of disease〔30〕.

The targeted agents ramucirumab and trastuzumab have been introduced into the therapy of patients with metastatic adenocarcinoma of the gastroesophageal junction, but the activity of these

drugs is limited〔31,32〕. The data to support the immunotherapy in patients with primary and (or) recurrent carcinoma of esophagus is currently limited, although several studies are ongoing. In the case of asymptomatic recurrence, there is also an option to observe the patient and intervene at the time of the manifestation of symptoms, taking into account the marginal survival benefit of palliative treatment for recurrent disease. However this option may not be acceptable for a number of the patients must always be one of the principal considerations during the decision on the selection of an appropriate treatment strategy.

To-day, SBRT utilizing conventional linear accelerators is a rapidly evolving technique in the world that, due to low toxicity and a short overall treatment time, may be considered an ideal therapeutic option for patients with a poor prognosis, such as those with recurrent esophageal carcinoma in whom the balance between quality of life and treatment toxicity should be carefully evaluated. Now the utilization of SBRT has been widely reported in patients with primary lung cancer, primary liver cancer and metastatic disease, and in individuals with recurrences of gynecological tumors and even brain metastases, with SBRT quickly becoming a standard institutional treatment worldwide in the future〔35〕. 〔33,34〕, However, there are few studies describing the use of SBRT in locally recurrent esophageal cancer without distant metastases, and further studies are required to clarify the optimal treatment approach in this type of patients〔36〕. SBRT currently is reversed for difficult clinical situations, that is, either recurrent disease after prior irradiation or tumor too large or anatomically difficult for brady-therapy and when these patients have no other treatment option 〔37〕.

Conclusion:

Recent clinical trials have established the optimal outcome that neoadjuvant or adjuvant treatment is effective in treating the locally advanced esophageal cancers. Moreover, radiation therapy serves an important role in these treatments. In our results, SBRT is a technically feasible and safe option for patients with locally recurrent esophageal carcinoma that provides the possibility of local control and a good quality of life during and after the treatment〔35〕. Now stereo-tactile radiotherapy should be used to treat various cancers, for example, recurrent cervical cancers, basal cell carcinoma of eyelid, and prostatic cancer〔40,41,42〕.

In the future, modern and upcoming radiotherapy technologies include image guidance, particle therapy, and MRI-guided radiotherapy, all of which show promise in allowing better soft tissue delineation, more precise radiation delivery, tumor tracking and gating during radiotherapy to spare normal tissue, and real-time adaptive radiotherapy to minimize doses to critical structures due to daily anatomies changes.

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