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Radiation Therapy for Esophageal Cancer

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Abstract

Esophageal cancer develops in the mucosa of the esophagus and spreads toward the muscle layer. The nonsurgical treatment for localized, deeply invasive esophageal cancer has been external beam radiation therapy (EBRT) and concurrent chemotherapy. Recently, intraluminal brachytherapy showed a strong potential for the improvement of the therapeutic ratio. It was found that the fractionated high dose rate (HDR) brachytherapy offered beneficial palliation for a longer period of time with more durable symptom control. A similar was concluded for advanced unresectable esophageal cancer in previously irradiated patients. HDR brachytherapy may be a useful salvage treatment option for inoperable patients diagnosed with local esophageal cancer. Although better local control can be achieved with higher brachytherapy dose, this increases the risk of acute morbidity and late morbidity, especially in the setting of recurrence cancer. It was found that the moderate dose of EBRT and HDR brachytherapy could give a better local response than EBRT alone.

Keywords: esophageal cancer, radiation therapy, brachytherapy

1. Introduction

Esophageal cancer is the eighth most common cancer worldwide, besides being the sixth most common cause of cancer death. There were 456,000 new cases in the world in 2012 [1]. It is four times more common in men than in women; it occurs more frequently among people above 45 years of age and reaches its plateau among people at 65–74 years of age. Its mortality is high; it can be as high as 84%. For the locally advanced disease, the 5-year survival

is 15–34%. The cornerstone of treatment remains surgery; however, there is evidence that survival is favorably influenced when additional therapies, such as chemotherapy or radiation therapy or their combination, or targeted therapies are used for lymph node-positive or cT2 or tumors that are larger than cT2. The clinical studies assessing treatment modalities for esophageal cancer are diverse: the modalities (chemotherapy, radiation therapy and surgery) have been evaluated in various orders and combinations. The number of study subjects has rarely been over 100 per study. The study populations have not always been homogeneous; different portions of the esophagus were affected, and the study population is sometimes mixed, regarding staging and histology.

1.1. Histology

Histology is usually based on the histologic analysis of an endoscopic sample. There are two main types of esophageal cancer: squamous cell carcinoma (SCC) and adenocarcinoma. Squamous cell carcinoma mostly occurs in the lining in the upper portion of the esophagus. Adenocarcinoma develops at the junction between the esophagus and the stomach. Most of the tumors are squamous cell carcinoma, but the incidence of adenocarcinoma has been increasing.

1.2. Predisposing factors

Intraepithelial neoplasias, such as epithelial dysplasias and in situ carcinoma, are the most significant precursor lesions for the development of esophageal cancer. Generally, it occurs a decade prior to carcinoma. The classification of dysplasias is based on the extent of the epithelial involvement. Some of the dysplasias show spontaneous regression. Nearly 30% of the severe dysplasias become invasive cancer. Tobacco use and/or consuming alcohol predominantly increase the risk of esophageal squamous cell carcinoma. Being overweight and/or reflux disease can primarily increase the risk of esophageal adenocarcinoma.

The multifocal appearance and intramural spread are common characteristics of esophageal cancer. It often spreads through the lymphatic system. Tumors involving the proximal portion of the esophagus may give metastases to the cervical lymph nodes, and tumors involving the lower portion may also give metastasis to the vicinity of the celiac artery. Cancer can infiltrate its surroundings, the pars membranacea of the trachea and the prevertebral fascia.

2. Treatment options

From a surgical point of view, early cancer means that the lesion only involves the mucosa and/or submucosa. The treatment option remains surgery for very early cancers (up to stage pT1b) while it is palliative in the case of metastatic esophageal cancer. For other cases, additional therapies, such as chemotherapy and/or radiation therapy may result in improved survival.

Regarding epidemiology, tumor biology, pathogenesis, and prognosis, the two main histological types of esophageal cancer, SCC and adenocarcinoma, are different from each other.

The perioperative mortality is higher for squamous cell cancer. It might be due to comorbidities and the localization of cancer since SCC mostly involves the upper third of the esophagus, and the postoperative mortality is significantly higher for esophageal cancer involving the proximal third. Esophageal cancer affecting the upper third and/or middle third of the esophagus recurs in a locoregional manner whereas adenocarcinoma can more often metastasize to distant sites. However, the prognosis of adenocarcinoma in an early stage is more favorable than that of SCC.

2.1. Chemoradiotherapy

The results of several randomized, phase III studies have been reported so far. Practically, a platinum-based medication is used in combination with radiation.

Morbidity and mortality are unclear regarding the use of neoadjuvant chemoradiotherapy. Some authors reported an increase in the anastomosis insufficiency and an increase in mortality, whereas others did not find an increase in mortality. A recent US study analyzed the data obtained from 1939 patients who had undergone esophagectomy. Seven hundred and eight patients received neoadjuvant therapy. They found no differences in mortality or morbidity [2]. The studies are unclear about the stage in which neoadjuvant therapy can be safely omitted. The American recommendation [3] states that neoadjuvant therapy is reasonable in the case of pT1b (>2 cm in size or dedifferentiated) whereas the European recommendation finds it reasonable only in stage T3-4 or lymph node-positive disease [4]. Chemoradiotherapy can be used

- Definitively: in inoperable cases or if the disease involves the upper third portion of the esophagus, with or without preventive, induction chemotherapy;
- In an adjuvant manner; or
- For a neoadjuvant purpose: if the patient is eligible for surgery (chemoradiotherapy, followed by surgery).

In a prospective multicenter study [5] with 186 patients with esophageal squamous cell carcinoma, three-year survival was significantly higher in patients receiving either pre-operative radiation or pre-operative chemotherapy, radiotherapy and surgery. Definitive chemoradiotherapy can be used in patients who are not surgical candidates or if the disease involves the proximal third portion of the esophagus. The main aims of care are to improve the quality of life and to maintain the patient's ability to swallow. The RTOG 8501 [6] study evaluated the benefits of concurrent chemotherapy compared to radiation therapy alone. The randomized portion of the study included 121 patients, and 61 were enrolled in the chemoradiation arm. No one had any distant metastases. Chemotherapy included the combination of continuous 5-fluorouracil (5-FU) and cisplatin. 1000 mg/m² of 5-FU was administered daily over 4 days during Week 1 and Week 5 of radiation treatment, as well as cisplatin at 75 mg/m² during the first day of Week 1 and Week 5 in combination with 50 Gy irradiation. After completion of radiation therapy, another two cycles were administered at unchanged doses. By contrast, 64 Gy irradiation was delivered as monotherapy in the other arm. Most of the patients (82%) had squamous cell carcinoma. The study proved the superiority of chemoradiotherapy over radiation therapy alone, regarding both median survival (12.5 vs. 8.9 months) and the 5-year

survival (26 vs. 0%). A PRODIGE-5/ACCORD-17 study [7] included 267 patients with up to IV/A stage esophageal cancer. Cisplatin and 5-FU used in the RTOG 8501 study were compared with the administration of six cycles of FOLFOX. FOLFOX + radiation yielded results similar to those of the regimen used in the RTOG study (median PFS: 9.7 vs. 9.4 months), but it was significantly less toxic.

Primarily, the combination of taxane and platinum was assessed in the neoadjuvant setup. The most commonly used paclitaxel (50 mg/m^2) and carboplatin (AUC2, weekly over 5 weeks) were at least as efficient as the combination of platinum and 5-FU [8]; therefore, it is accepted as definitive treatment. In general, definitive chemoradiation is a choice of treatment for those patients who are not suitable for surgery or who do not consent to surgery.

Since distant metastases are present nearly in 75% of patients with locally advanced esophageal cancer, induction chemotherapy prior to chemoradiotherapy would be a rational choice. Usually, patients with locally advanced but resectable esophageal cancer were enrolled in the studies. Since there are no phase III study results, these regimens have not become recommendations. Seventy-two patients participated in the phase II, RTOG 0113 study [9]. The induction treatment included 5-FU ($5 \times 700 \text{ mg/m}^2$), cisplatin ($5 \times 15 \text{ mg/m}^2$) and paclitaxel (200 mg/m^2) or cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2), which was followed by a similar combination (5-FU + paclitaxel or cisplatin + paclitaxel) administered simultaneously with a total radiation dose of 50.4 Gy. Median survival showed no significant differences, and the toxicity was similar in both arms.

Neoadjuvant chemoradiotherapy can be used in those patients who are suitable for surgery. The method of treatment is practically identical to that of the definitive chemoradiotherapy. The aim of the treatment of inoperable patients is palliative, and the aim is to improve the proportion of operability or recovery. The studies frequently yielded contradictory results. However, based on several clinical trials and meta-analyses, neoadjuvant chemoradiotherapy proved to be superior to surgery alone in patients with locally advanced esophageal cancer. A significant survival benefit was found in the CROSS study [10] in which 366 patients with potentially resectable esophageal or gastroesophageal junction cancer were randomized to get either preoperative chemoradiotherapy (50 mg/m^2 paclitaxel a week + carboplatin AUC2, concurrent radiotherapy with a total dose of 41.4 Gy over 5 weeks) or surgery alone. Patients tolerated the combined treatment well. There were no significant differences in mortality or morbidity. The complete resection rate was 92 vs. 69% in favor of the combined treatment, and the complete pathological remission (pCR) ratio was 29% in patients receiving chemoradiotherapy. There was a significant difference in median overall survival (preoperative chemoradiotherapy followed by surgery vs. surgery alone: 49.4 vs. 24.0 months).

In the FFCD 9901 study [11], the efficacy of preoperative chemoradiotherapy was evaluated in patients with small-sized, resectable tumors. 195 patients with stage I or II disease were randomized into the preoperative chemoradiation arm (two cycles of 5-FU at 800 mg/m^2 daily at Days 1–4 and 29–32, plus cisplatin at 75 mg/m^2 at Day 1 or Day 2 of the cycle, in both cycles, plus a total dose of 45 Gy concurrent radiation) or the surgery alone arm. During this study with a median follow-up of 93.6 months, there were no significant differences in the 3-year survival. No significant survival benefits were noted in any of the subgroups. Based on these data, the combined treatment may not result in any survival benefit.

Numerous meta-analyses have dealt with the comparison of the effects on survival regarding the trimodal treatment or surgery alone. One of the latest studies was published by Sjoquist and his colleagues [12]. It includes the twelve most significant neoadjuvant chemoradiation studies. The reducing effect of neoadjuvant chemoradiotherapy on mortality proved to be significant, which led to an absolute survival benefit of 8.7% after two years. It was independent of the histologic type of the tumor, and it was not associated with increased perioperative mortality, either.

In addition to the conventional cisplatin + 5-FU therapy, adding paclitaxel to platinum has become more popular lately. Results of ten studies were analyzed in another meta-analysis, and a comparison was made between the efficacy of paclitaxel together with platinum and the efficacy of platinum together with 5-FU. The analysis proved the benefit provided by neoadjuvant chemoradiation therapy over both combinations. The risk of mortality was significantly reduced with both chemotherapy combinations, but the benefit was more pronounced in the taxane arm. However, it was only statistically significant in the case of squamous cell cancer [8]. Some small-sized studies have found the combination of docetaxel and platinum effective [13, 14].

Based on the consequent results of several clinical studies, the response to perioperative treatment, especially the pCR, is an important indicator of better overall survival. Thus, intensification of the perioperative treatment could be a potential approach. Based on the results of 22 studies, survival of those patients who achieved pCR as a result of treatment was 2–3 times longer compared to those patients who had residual cancer in the resection specimen obtained via surgery following neoadjuvant chemoradiotherapy. During the intensification of neoadjuvant treatments, the employments of chemotherapy prior to chemoradiation, as well as the increase of the number of the agents have been studied. According to the INT0123 study, radiation dose intensification resulted in no improvement in either the survival or the local control [15].

Some work was conducted in relation to the non-surgical treatment options of patients with squamous cell carcinoma of the esophagus. Trimodal therapy (chemoradiotherapy followed by surgery) was compared with chemoradiotherapy by Stahl et al. and in the FFCD 9102 study. Stahl et al. [16] enrolled 172 patients. Patients received three cycles of bolus 5-FU, leucovorin, etoposide, cisplatin (FLEP) followed by chemoradiotherapy including a total dose of 40 Gy irradiation and cisplatin and etoposide chemotherapy. Patients then underwent either observation or surgery. In the surgery arm, 62 out of 86 patients underwent surgery. However, there were no significant differences in overall survival. The two-year progression-free survival was more beneficial for those patients who had undergone surgery (64.3 vs. 40.7%). Notably, both the radiation dose and the intensity of chemotherapy were lower than those used in conventional treatments. In the FFCD 9102 study [17], 259 patients with locally advanced, resectable SCC were randomized into two arms following low-dose chemoradiotherapy. If a therapeutic response was noted after the induction treatment, surgery was performed or chemoradiotherapy was completed. No significant differences were found in overall survival between the two treatment groups. However, the 3-month mortality was significantly higher ($p = 0.002$) in the surgery arm (9.3 vs. 0.8%).

Little is known about the results of the nonsurgical treatment of patients with adenocarcinoma. Based on a retrospective analysis of the results of 276 patients treated with definitive chemoradiotherapy for esophageal adenocarcinoma at the university of Texas MD Anderson cancer center [18]. After a median follow-up of 54.3 months, 33.3% of the patients never had a relapse. Local relapse was present in 51% of the patients, and distant dissemination was detected in 43.5% of the patients.

There are not enough phase III results in relation to adjuvant chemoradiation. In a retrospective study by Bedard et al. [19], data of 38 patients who had undergone surgery for node-positive esophageal cancer, had received postoperative adjuvant chemoradiation (concurrent or sequential radiation therapy plus cisplatin and 5-FU \pm epirubicin) were compared with data of patients who had undergone surgery only. Both the local control and median survival proved to be better in patients receiving adjuvant treatment, and so did overall survival. In another retrospective analysis [20], benefits of adjuvant chemoradiation were evaluated in 304 patients who had undergone surgery for node-positive esophageal squamous cell cancer. Based on the data, both the 5-year overall survival and the disease control proved significantly better in patients who had also received chemotherapy in addition to radiotherapy. According to a prospective study [21] that evaluated chemoradiation vs. chemotherapy and included 45 patients, neither survival benefit nor improved locoregional control was shown in the chemoradiation treatment arm relative to chemotherapy alone (cisplatin + 5-FU over 5 weeks plus 50 Gy of irradiation over 5 weeks vs. cisplatin + 5-FU over 5 weeks).

2.1.1. Neoadjuvant chemotherapy

Eight hundred and two patients with either SCC or adenocarcinoma were randomized in the MRC OEO2 study [22]. Patients received either two cycles of cisplatin + 5-FU preoperatively or underwent surgery primarily. The 5-year overall survival was 23 vs. 17% in favor of the neoadjuvant treatment regimen. In Sjoquist's meta-analysis, data of 1981 patients were assessed. Nine neoadjuvant chemotherapies were compared to surgery alone [12]. Chemotherapy reduced mortality in the entire patient population receiving neoadjuvant chemotherapy. It was significant in patients with adenocarcinoma. Based on these, neoadjuvant chemotherapy seems to be superior to surgery alone.

It is unclear whether neoadjuvant chemotherapy can be an alternative to neoadjuvant chemoradiation therapy. Stahl et al. [23] enrolled 119 patients with adenocarcinoma involving the lower third portion of the esophagus or the gastroesophageal junction. In one of the arms, patients received 15 weeks of chemotherapy (cisplatin + leucovorin + continuous 5-FU) followed by surgery. In the other arm, 12 weeks of chemotherapy were followed by concurrent chemoradiation therapy (low-dose radiation therapy and concurrent cisplatin + etoposide) over 3 weeks, and surgery was then performed. The ratio of pCR was significantly higher in the arm that included chemoradiation therapy (2 vs. 15.6%). However, there were no significant differences in median survival and the 3-year overall survival between the two treatment arms. Burmeister et al. [24] received similar results when they evaluated 75 patients with adenocarcinoma. Regarding pCR and R1 resection, chemoradiotherapy was significantly more beneficial, but there were no significant differences in median survival.

Briefly, chemotherapy can be employed as part of chemoradiation, in a neoadjuvant manner, in an adjuvant manner, or as palliation in metastatic disease.

3. Brachytherapy of esophageal cancer

The results in a large cohort of patients indicated that HDR brachytherapy alone was an effective method for the palliation of advanced esophageal cancer [25]. Similar long-term results were reported in favor of treatments involving concurrent chemoradiotherapy followed by HDR brachytherapy [26]. Although brachytherapy was found to be preferable, there are studies (such as Refs. [27, 28]) suggesting the stent placement may play an important role for the palliation of disease. In that case, the prognostic models were used as evidence-based tools in decision making. However, the health-related life quality was reported to be improved in patients treated with the HDR brachytherapy. Recent studies suggested the usage of Californium-252 neutron brachytherapy combined with EBRT for esophageal cancer. The treatment resulted in favorable local control and long-term survival rates with tolerable side effects [29]. Patient selection, timing of brachytherapy and dose specifications were well documented [30–32]. Clinicians continue to urge caution in using brachytherapy treatment techniques since severe toxicity can occur post treatment [15, 26, 30]. Therefore, the addition of brachytherapy, with consequently high surface doses, should be limited to well-selected patients [33].

For that reason, the clinical implementation and accuracy in dose delivery is crucial for favorable treatment outcomes. The radiation dose is delivered using esophageal transoral or transnasal applicators with an external diameter of 0.6–1 cm. Ideally, the single channel applicator needs to be placed centrally in the lumen of the esophagus; however, there exists a possibility that the applicator will be closer to one side of the lumen, delivering a larger dose to the epithelium, lamina propria and muscularis mucosa, resulting in local esophageal complications. In those cases, stricture formation, fistula and esophageal ulceration are the common late toxicities of HDR brachytherapy [34]. A possible difference in the delivered dose is caused by disagreements in the choice of the dose point (i.e. mucosal surface or certain distance from the central line of the applicator) in various institutions, as reported in Ref. [35]. For instance, it was reported in the long-term experience with esophageal brachytherapy treatment [36] that radiation was delivered at a level of 5 mm below the surface of the mucosa. However, no correlation was found between the post-treatment complications and the diameter of the brachytherapy applicator [37]. In most of the HDR brachytherapy treatments, 3D treatment plans were generated using computed tomography (CT) images; however, magnetic resonance imaging (MRI) can be used to assist the localization of the tumor and the applicator [38]. The treatment planning for the esophageal cancer patient is performed using the TG-43 formalism [39], since the dose calculation accuracy of the TPS was confirmed in a homogeneous medium [40].

Overall, this HDR treatment is demonstrated to be well-tolerated and effective for superficial primary and recurrent esophageal cancer in inoperable patients [41, 42]. The authors concluded

that dose escalation with larger diameter applicators may allow for improved therapeutic coverage without exceeding the organs at risk tolerances [43]. The latest research in the combined approach (EBRT and HDR) to palliation in esophageal cancer together with the review of the current techniques is reported in Refs. [44, 45].

3.1. Clinical implementation

To decrease the dose to the organs at risk in the upper gastrointestinal region a novel disposable brachytherapy transoral balloon centering esophageal applicator (BCEA) with five independently inflatable balloons was developed [44]. The complete treatment process for this applicator consisted of three principal steps: pre-treatment preparation, treatment planning and treatment delivery (**Figure 1**). This applicator allows for the central placement of the radioactive source during treatment. The BCEA allows for the treatments outside the balloon region with the constraint where the BCEA becomes similar to the standard esophageal applicator (EA).

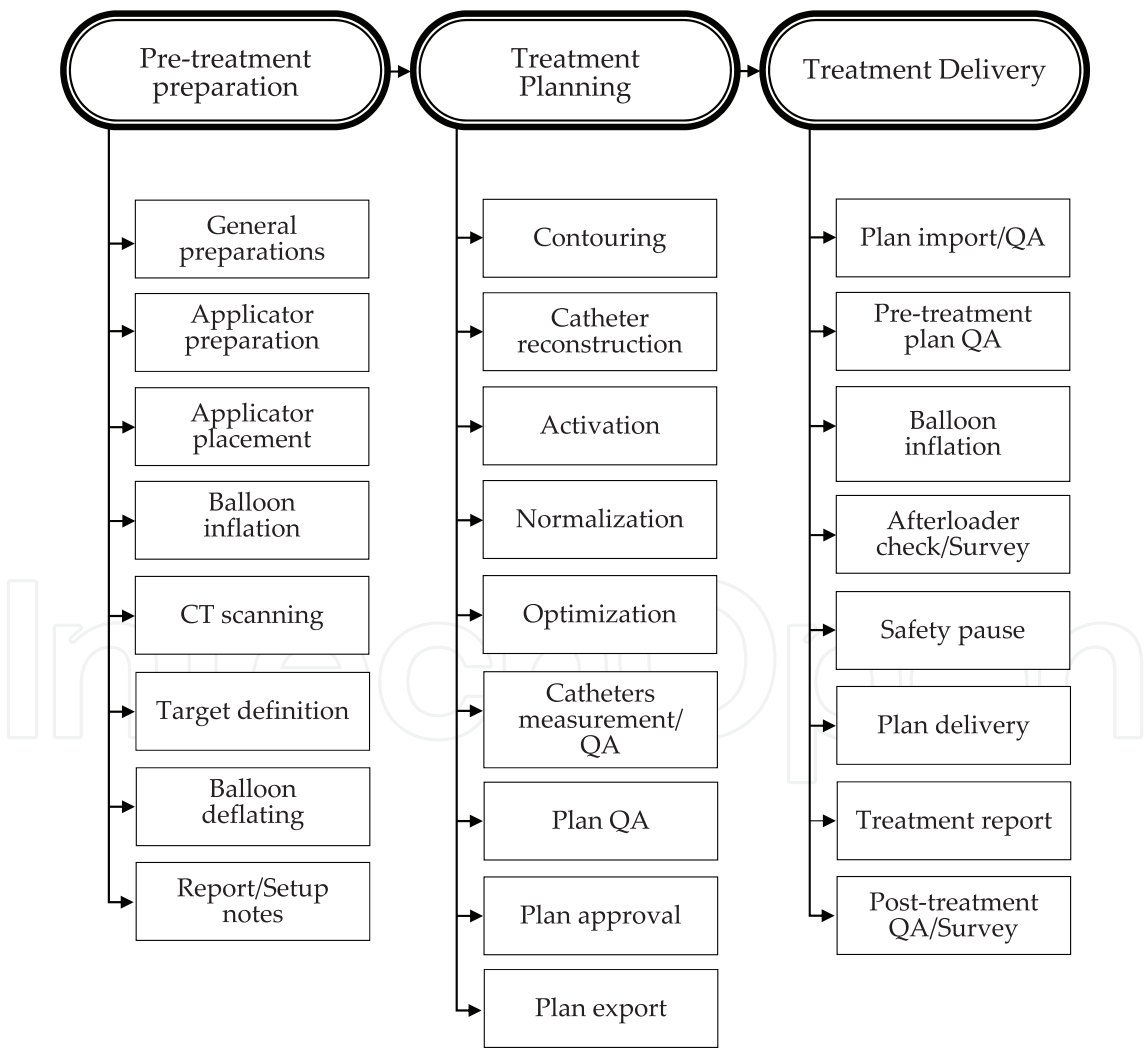


Figure 1. The detailed process map of the treatment was developed for improved treatment plan generation and quality assurance of the process.

The experience in the treatment of esophageal cancer using a standard intraluminal esophageal applicator (EA) was summarized in Ref. [45]. Unlike with the transnasal insertion (EA) where the endoscope would be placed via the anesthetized nose past turbinates and nasopharynx behind the larynx and into the esophagus, the BCEA is placed transorally.

3.2. Treatment planning and delivery

The BCEA positions the catheter centrally when the balloons are inflated. Due to that fact, the treatment plan can be additionally optimized (not the case for the standard EA) for improved dose distribution and conformality. The treatment length was defined as a pretreatment tumor length with 1–2 cm distal and proximal margin determined by pretreatment imaging and confirmed by the CT images.

The prescription dose is usually planned to be delivered to the diameter of 1 cm with respect to the central catheter with an additional optimization to avoid the critical anatomical structures such as the heart, lung, pharyngeal constrictor and spine. The dose calculation is performed using the TG-43 formalism that includes the anisotropy corrections. With the standard EA, the dose point is defined at the mucosal surface or a certain distance from the central line of the applicator with identical dwell times along the treatment length. This was mostly done to minimize the uncertainties in dose delivery related to the positioning of the EA inside the esophagus. In standard approach when EA is used the dose optimization outside the balloon region should be avoided due to the complicated position reproducibility. **Figure 2** shows the differences in the treatment plans between the EA and BCEA.

The centrally placed catheter inside the esophagus lumen resulted in enhanced dose distribution and reproducibility in multi fractional treatment (**Figure 2**). The position of the applicator and the balloon diameters can be verified before the treatments using the planning CT images and the CT images obtained prior to each fraction. Three methods can be used to verify the

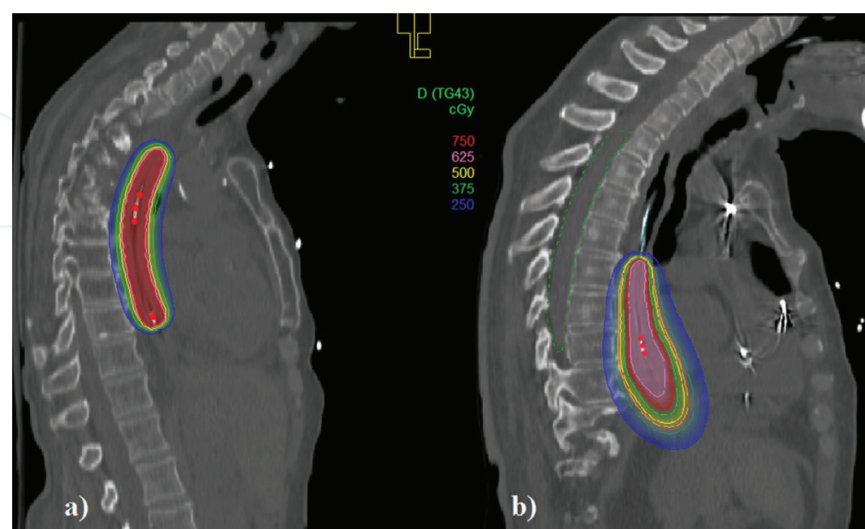


Figure 2. Sagittal images show: (a) the non-optimized plan using the EA and (b) optimized dose distribution achieved with the BCEA.

proper positioning of the BCEA prior to each treatment: (a) using an external marker to verify the length of the catheter in the patient, (b) evaluation of the position of 12 radio-opaque markers on the exterior side of the catheter in the CT images, and (c) measurements of the diameters of the balloons on CT images after inflation to confirm that they were properly inflated.

4. Conclusion

In this chapter, various aspects of esophageal cancers were discussed such as histology, predisposing factors and treatment options. It was found that the moderate dose of EBRT and HDR brachytherapy could give a better local response than EBRT alone. Therefore, the brachytherapy of esophageal cancer was elaborated in more detail.

Classically, one of the limitations for the deployment of esophageal brachytherapy has been the difficulties associated with the placement and tolerance of the transnasal applicator [44]. The common adverse effects included significant pain on placement and for the duration of its indwelling. Nasal bleeding, often significant, can be seen from both the scope and catheter placement. There is often the need of significant pain medicine to tolerate this procedure. These effects are pronounced if the applicator is kept in place for an extended period of time.

Long-term toxicities and the correlation between the formation of a fistula or ulceration and the novel design of the BCEA are the topics that can be additionally investigated using the data of more patients treated with the novel BCEA and longer follow-up. Due to the limited number of patients, it is not yet possible to conclude if the patients benefit from the treatment using the centrally placed applicator. Furthermore, due to the provision to additionally optimize the dose, there exists a possibility of dose escalations for certain patients, depending on their anatomy and the spread of disease. The initial implementation of this applicator required strict and careful testing, especially in the determination of the accurate treatment length that would allow the radioactive source to be sent to the most distal position (first dwell position). Multiple tests and an interobserver agreement are required since the inaccurate results of this test can potentially offset the whole treatment, causing adverse events. Therefore, the treatment length and BCEA applicator positioning should be evaluated before each fraction.

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