Chapter

External Beam Radiotherapy in Differentiated Thyroid Cancer

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Abstract

Differentiated thyroid cancer is treated by surgery, radioiodine treatment, and Thyroid Stimulating Hormone (TSH) suppression. The role of external beam radiotherapy is mainly palliation of radio-iodine non avid metastatic lesions and in inoperable tumors. Metastasis involving weight-bearing bones and vertebral metastasis with impending spinal cord compression are primarily treated by external radiation. External Beam Radiotherapy improves loco-regional control in patients with gross residual disease after surgical resection. Patients with extra-thyroidal disease and positive margins are treated by adjuvant external beam radiotherapy, especially when the post op radio-iodine scan is negative. External beam radiotherapy is the treatment of choice for radio-iodine non avid inoperable loco-regional recurrence. SRS alone or surgery followed by SRS is the preferred treatment for solitary brain metastasis. Whole brain radiotherapy is the treatment of choice for multiple brain metastatic disease.

Keywords: differentiated thyroid cancer, external beam radiotherapy, iodine refractory disease

1. Introduction

Differentiated thyroid cancer (DTC) is treated by surgery, thyroid stimulating hormone (TSH) suppression, and radioiodine therapy according to the risk stratification [1, 2]. External Beam Radiotherapy (EBRT) is used in selected patients in the adjuvant setting. EBRT is mainly used in the palliation of radio-iodine non-avid metastatic disease and inoperable tumors. There are no prospective randomized trials on EBRT in DTC. The available evidence is from single institution retrospective studies, systematic reviews, and meta-analysis. In this chapter, we discuss the role of EBRT in localized and metastatic DTC. **Figure 1** summarizes the role of EBRT in differentiated thyroid cancer.

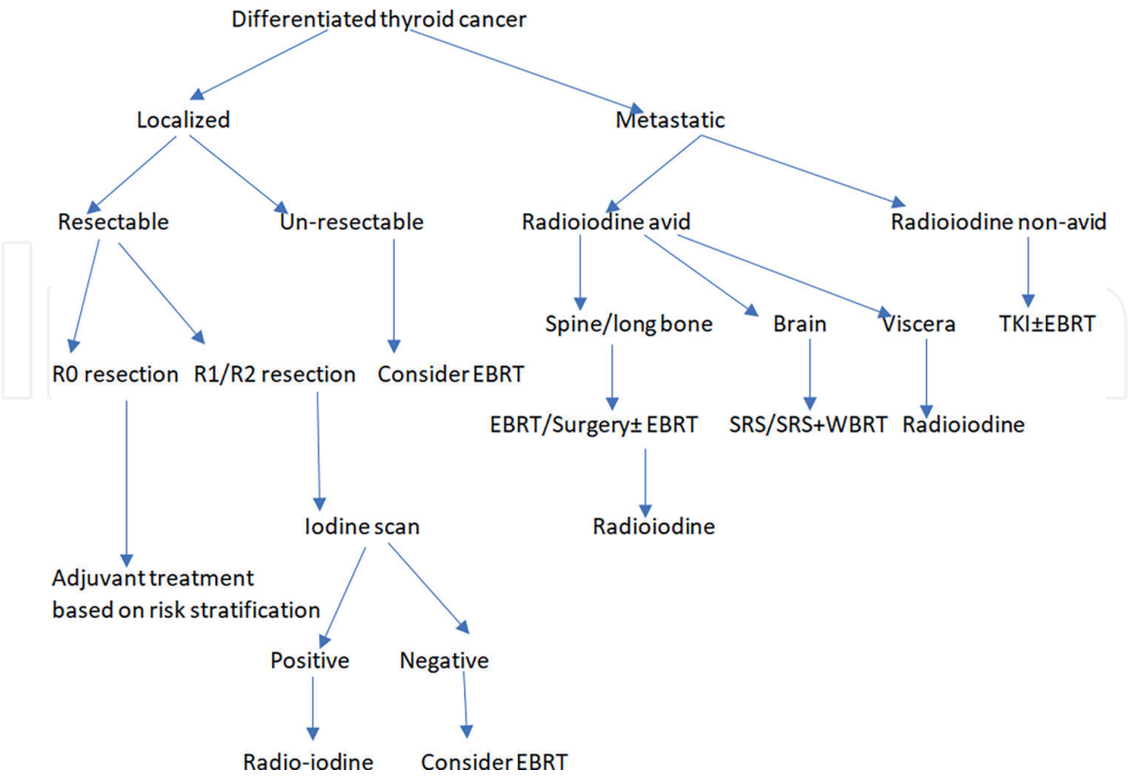

Figure 1.
The role of EBRT in differentiated thyroid cancer.

2. Localized disease

2.1 Gross loco-regional residual disease after surgery

The definition of gross residual disease is not clearly defined in the published literature. EBRT improves loco-regional control in patients with gross residual disease after surgical resection. Most of the retrospective studies utilized radio-iodine in addition to EBRT. Hence the magnitude of benefit from EBRT alone is not known. In patients less than 55 years old with limited radio-iodine avid gross residual disease, EBRT is not indicated as radio-iodine alone may be sufficient for local control. In patients with radio-iodine concentrating residual disease, radio-iodine treatment is considered first and EBRT is given after radio-iodine to avoid the stunning effect of EBRT. EBRT is considered before radioiodine treatment in cases where the residual disease is likely to compromise the airway.

In a retrospective study from Queen Elizabeth hospital China with 842 patients, EBRT was effective in increasing local control in patients with gross residual disease [3]. At Memorial Sloan Kettering Cancer Center, 2 and 4 year loco-regional control with EBRT was 77% and 62%, respectively, for patients with gross residual disease [4]. Meadows et al. reported 5 year local control rate of 70% for patients with gross residual disease [5]. In a retrospective study, Sia et al. reported 10 year local relapse free rate of 90% with EBRT for those with gross residual disease [6]. Beckham et al. have reported the outcome of DTC patients treated with IMRT and concurrent Doxorubicin in patients with un-resectable and gross residual disease. Patients who received concurrent chemotherapy had better local progression-free survival and

overall survival than those who received only IMRT [7]. EBRT is primarily considered for macroscopic residual disease in case of radio-iodine non avid residual disease. EBRT may be considered after radio-iodine treatment if the residual disease is unlikely to be controlled with radio-iodine treatment alone.

2.2 T4 disease after complete surgical resection or microscopic margin positivity

Radio-iodine is the treatment of choice for extra-thyroidal extension and microscopic positive margins. EBRT is not routinely recommended in this scenario. EBRT may be recommended in patients with microscopic residual disease and aggressive histological subtypes which are unlikely to concentrate iodine.

A randomized control trial was designed in Germany with pT4 patients in the EBRT arm and no EBRT arm, but due to poor accrual it was converted into a prospective cohort study. The RT dose to the thyroid bed was 59.4Gy for R0 resection and 66.6Gy for R1 resection. The complete remission rate was 96% with EBRT versus 86% without EBRT, and the study concluded that EBRT could not be routinely recommended for all pT4 disease [8]. Schwartz et al. reported a loco-regional control rate of 81% after EBRT in patients with extra-thyroidal disease or microscopic positive margins [9]. The median dose was 60 Gy for negative margins or microscopic positive margins. Over a 40-year period, Princess Margaret Hospital experience demonstrated benefit in LRC with EBRT of 45–50 Gy for patients >60 years, T4 disease without gross residue [10]. Kim et al. reported improvement in LRC for T4 or node positive disease with EBRT doses of 50–70 Gy [11]. The role of EBRT in patients with tracheal invasion was reported by Keum et al. and Kim et al. in 2 separate publications. Both these studies reported superior loco-regional control with EBRT [12, 13]. In another retrospective study by Groen et al., 5 year LRC was 84.3% with EBRT (66 Gy) for microscopic residual disease [14].

EBRT may be considered for patients with extra-thyroidal extension or microscopic positive margins that are radio-iodine non-avid.

2.3 Un-resectable DTC

Palliative EBRT is recommended to relieve symptoms in un-resectable DTC [15]. In a retrospective cohort study by Carrillo et al., un-resectable DTC patients were treated with EBRT or EBRT followed by salvage surgery. Patients with ECOG performance status≤2 received doses above 56 Gy and a palliative dose of 30–50 Gy was used for patients with poor performance status. IMRT followed by salvage surgery was associated with increased Progression Free Survival and Overall Survival [16].

2.4 Inoperable loco-regional recurrence

The most common sites of failure in DTC are the thyroid bed and regional nodes. The treatment of choice for loco-regional recurrence is salvage surgery followed by radioiodine treatment. EBRT is considered after surgery when there is extensive extra-thyroidal extension or extra-capsular spread of lymphnodes at recurrence [17]. Some patients may develop loco-regional recurrence not amenable to surgery or radio-iodine. EBRT is the preferred treatment modality in such cases [4, 18]. The dose ranges from 66 to 70 Gy.

2.5 Evidence from systematic reviews and meta-analysis

A systematic review of 16 studies by Fussy et al. reported an improvement in LRC with post-op EBRT in patients at high risk for recurrence and above 45 years of age [19]. Another systematic review and meta-analysis by Dicuonzo et al. also reported improvement in loco-regional control with the addition of EBRT to surgery and radio-iodine without considerable toxicity [20]. Jacomina et al. conducted a systematic review and meta-analysis of 9 trials and reported improvement in 5 year loco-regional recurrence free survival with post-operative EBRT in patients with advanced age, gross or microscopic residual disease, and loco-regionally advanced disease. However, there was no improvement in overall survival or distant metastasis failure-free survival [21]. A recent review by Roukoz and Gregoire concluded that adjuvant EBRT reduces the risk of loco-regional recurrence in locally advanced DTC with high-risk features [22].

2.6 Radiotherapy-Pretreatment evaluation, technique, dose, and volumes

Dental, speech, swallowing, and nutritional evaluation should be done prior to radiotherapy. Pre-treatment contrast enhanced CT, MRI, and whole body iodine scans can be used for delineation of target volumes. The target volumes should include any gross residual disease, the thyroid bed, including the trachea-esophageal grove and draining lymph nodes (peri-thyroidal lymph nodes, para-tracheal, pre-tracheal, superior mediastinum and cervical lymph nodes). PET CT helps in the delineation of gross tumors, especially in iodine refractory disease [23]. Intensity Modulated Radiotherapy (IMRT) is the technique of choice for EBRT in DTC [7, 24–26]. IMRT ensures appropriate coverage of volumes and it spares more normal tissues compared to 3 Dimensional Conformal Radiotherapy. It also allows for dose escalation without increasing toxicity [27]. The recommended EBRT dose is 66–70 Gy for gross residual or un-resectable disease, 60–66 Gy for microscopic disease, and 50–56 Gy for elective nodal regions [28, 29]. Gross residual nodes are treated with 66–70 Gy and nodes with extra-capsular extension are treated with 60–66 Gy.

2.7 Radiotherapy toxicities

Acute toxicities of radiotherapy include skin erythema, desquamation, mucositis, and dysphagia. Esophageal and tracheal stenosis, chronic dysphagia, feeding tube dependency, and xerostomia are the late side effects. According to the study by Schuck et al., acute grade 3 toxicity in the larynx, pharynx, and skin of any grade was reported in only 9.1% of patients and there were no late grade 3 toxicities after EBRT [30].

3. Metastatic disease

The EBRT is used for symptomatic metastatic disease that is not amenable to surgery or radio-iodine. The most common sites of metastases from DTC are bone and lungs. Radio-iodine-avid metastatic bone lesions are treated by radio-iodine. Palliative surgery is recommended for patients who have a pathological fracture or spinal cord compression and a limited volume of metastatic disease. EBRT is used to complement surgery in such situations [31]. EBRT is primarily considered in cases of metastases involving weight-bearing bones and vertebrae with impending spinal

cord compression [32]. Stereotactic radiosurgery is effective for oligo-metastatic bone lesions [33–35]. Due to prolonged survival in DTC, hypo fractionated regimens like 40 Gy in 15 fractions or 30 Gy in 10 fractions are recommended. Less protracted regimens like 20 Gy in 5 fractions or 8 Gy single fraction EBRT can be considered in patients with disseminated metastatic disease [36]. Multiple cerebral metastases are usually treated by whole brain RT (30 Gy in 10 fractions or 20 Gy in 5 fractions) as radio-iodine is likely to aggravate cerebral edema [37]. Solitary brain metastasis is treated by surgical excision or stereotactic radiosurgery (SRS). Surgical excision followed by SRS or SRS alone can be considered for ≤4 brain metastases [36]. SRS is reported to be safe in patients with DTC and it results in durable intracranial disease control [38]. The systemic treatment of choice for iodine refractory metastatic differentiated thyroid cancer is tyrosine kinase inhibitors (TKI). Sorafenib and Lenvatinib are approved for the treatment of iodine refractory disease in the first line setting [39, 40]. Cabozantinib is approved for patients previously treated with vascular endothelial growth factor receptor (VEGFR)-targeted therapy [41]. At present, there is no concrete data to alter the indication for palliative radiotherapy in metastatic disease in the TKI era.

4. Future directions

EBRT is the treatment of choice for iodine refractory DTC recurrence. A pilot study conducted on F18 FDG PET guided EBRT showed promising results [42]. PETCT identifies relapsed sites and allows dose escalation to sites of recurrence. It helps in reducing treatment volumes, thereby reducing adverse effects. Initial experience on Intensity Modulated Proton Therapy (IMPT) from Mayo Clinic has been published and showed promising loco-regional control for recurrent iodine refractory DTC [43, 44]. The long term efficacy and safety of proton beam therapy are yet to be proven.

5. Conclusions

EBRT reduces the risk of loco-regional recurrence in locally advanced DTC. EBRT is indicated in gross loco-regional residual disease after surgery, extra-thyroidal extension with radioiodine non avid microscopic residual disease, inoperable loco-regional recurrence which fails to concentrate iodine; and in the palliation of metastatic disease.

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