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The role of external beam radiation therapy in thyroid cancer: when and how to do it

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ABSTRACT

External beam radiation therapy (EBRT) involves using high-energy X-rays or particle beams targeted at malignant tissues, with the goal of destroying tumor cells while minimizing damage to healthy surrounding structures. However, the indication and timing of EBRT vary considerably depending on the specific histological subtype of thyroid cancer, the presence of metastatic or unresectable lesions, and individual patient factors such as comorbidities and prior treatments. Moreover, the therapeutic benefit of EBRT must be balanced against potential side effects, making patient selection and protocol design pivotal components in managing advanced thyroid cancer. This article explores the role of EBRT in thyroid cancer, with particular attention to when it is recommended, the patient populations that benefit most, and how to optimize treatment protocols. By illuminating current best practices and emerging evidence, we aim to guide clinicians in deciding when and how to incorporate EBRT into a multidisciplinary treatment plan for thyroid cancer.

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Introduction

Thyroid cancer is the most common endocrine malignancy worldwide. According to GLOBOCAN 2020, it accounted for 3.0% of the 19.3 million new cancer cases and 0.4% of the 10.0 million cancer-related deaths globally. Its incidence showed a rising trend compared with data from 2018. While thyroid cancer ranked ninth in the number of new cancer cases, it was twenty-fourth in mortality, underscoring its relatively favorable prognosis, high cure rates, and excellent survival. In Pakistan specifically, there were 2,762 new thyroid cancer cases and 578 related deaths in 2020, with a 5-year prevalence of 6,578 cases [1].

Women are more likely than men to develop thyroid cancer. In 2020, the age-standardized incidence rates were 10.1 per 100,000 women and 3.1 per 100,000 men, while age-standardized mortality rates were 0.5 per 100,000 women and 0.3 per 100,000 men [2]. Approximately 65% of thyroid cancer patients present with localized disease, 30% with regional involvement, and fewer than 5% with distant metastases. Correspondingly, the 5-year relative survival rates for localized, regional, and distant disease are 99.9%, 98.3%, and 53.3%, respectively [3].

Thyroid cancer is generally managed with surgery and radioactive iodine therapy. While these standard treatments - particularly complete surgical resection and radioactive iodine ablation - are highly effective for well-differentiated thyroid cancers (DTCs), certain patients either present with or develop more advanced, refractory disease. In such cases, external beam radiation therapy (EBRT) becomes an indispensable component of the therapeutic strategy (Table 1).

Role of EBRT in DTC

Treatment overview

DTC is primarily managed with surgery, TSH suppression, and radioactive iodine-131 (RAI-131) therapy, guided by individual risk stratification. In certain cases, EBRT is used as an adjuvant therapy, particularly for radioiodine non-avid metastatic disease or unresectable lesions [4,5]. Evidence for EBRT's role in DTC primarily stems from single-institution retrospective studies, systematic literature reviews, and meta-analyses, as no prospective randomized controlled trials have been conducted to date.

EBRT may be considered in patients with gross residual disease, extrathyroidal extension (ETE), positive margins, or unresectable and inoperable recurrent disease.

EBRT in gross loco-regional residual disease after surgery

EBRT enhances loco-regional control (LRC) in patients with gross residual disease post-surgical resection. Most retrospective studies included EBRT and RAI-131 therapy as part of treatment, making it difficult to determine the precise benefit of EBRT alone. RAI treatment is prioritized in patients with RAI-avid residual disease to avoid the stunning effect of EBRT. When a patient's airway is at risk due to a residual tumor, EBRT is given priority. A retrospective study of 842 patients with papillary thyroid cancer at Queen Elizabeth Hospital (1960-1997) found that patients with gross postoperative local residual disease benefited most from RT in terms of local control (RR = 0.36) [6]. Another study from Memorial Sloan Kettering Cancer Center on 76 patients with non-anaplastic thyroid carcinoma reported a 2-year and 4-year overall LRC rate of 86% and 72%, respectively, and overall survival (OS) rates of 74% and 55% for all patients. These were high-risk patients since 84% had T4 disease and 79% of them had positive nodes [7].

EBRT in extra-thyroidal extension and positive margins

Radio-iodine is the preferred treatment for ETE and microscopic positive margins (R1), and EBRT is usually not recommended. However, in locally advanced cases, specifically in patients over 60 years of age with T4 disease, retrospective analysis revealed that adjuvant post-op RT increased LRC [8]. A German randomized control trial that converted into a prospective cohort study due to insufficient enrollment showed a complete remission rate of 96% with EBRT versus 86% without it [9]. A retrospective cohort study at the University of Texas MD Anderson Cancer Center on 88 patients with T4a differentiated thyroid carcinoma revealed that 5-year disease-free survival (DFS) was 43% for RAI alone and 57% for RAI with EBRT, with age and esophageal invasion as independent predictors of lower DFS [10].

EBRT in unresectable thyroid carcinoma

The UK National Multidisciplinary Guidelines recommend palliative EBRT to alleviate symptoms in unresectable DTC [11]. A STROBE-compliant retrospective cohort study of unresectable DTC patients treated with EBRT (16 patients) or EBRT followed by salvage surgery (17 patients) revealed that radiation therapy resulted in a higher response rate that enabled successful salvage surgery, increasing DFS and OS. However, this was a small study, and a larger, randomized trial with more patients is needed to determine the precise benefits of EBRT added as a neo-adjuvant therapy in circumstances where surgery is not an option [12].

Table 1. *Indications of radiation therapy in CA thyroid.*

Indications of RT in DTC	Gross residual Aerodijestive invasion Unresectable Inoperable recurrence Palliation of metastatic disease
Indications of RT in MTC	Gross residual Recurrent disease Palliation of metastatic disease
Indications of RT in ATC	Adjuvant radical treatment Palliation of metastatic disease

EBRT in inoperable loco-regional recurrences

Salvage surgery followed by RAI is preferred for thyroid bed and regional nodes failures. EBRT is considered for significant extra-thyroidal spread and positive nodes with extra-capsular dissemination [13]. For unresectable recurrences, EBRT is typically the treatment of choice with doses varying between 66 and 70 Gy [11,14].

Evidence from systematic reviews and meta-analyses

A comprehensive review revealed that high-risk patients over 45 years of age showed improved LRC with RT [15]. Another meta-analysis suggested that patients with high recurrence risk, such as those with T4, node-positive, margin-positive, and gross residual disease, may benefit from EBRT [16].

EBRT in metastatic disease

The most frequent areas of DTC metastasis are the bone and lungs. Iodine-131 is used to treat RAI-avid metastatic bone lesions. Surgical stabilization is recommended for patients with pathological fractures or spinal cord compression, followed by palliative RT. RT is also used to treat symptomatic metastatic disease that cannot be treated with surgery or radio-iodine. For oligo-metastatic bone lesions, stereotactic radiosurgery (SRS) is often used. Because of the better survivals even in metastatic DTC, hypo fractionated regimens such as 40 Gy in 15 fractions or 30 Gy in 10 fractions are advised. In patients with extensive metastasis, 20 Gy in 5 fractions or 8 Gy in a single fraction can be administered [17].

Because RAI is prone to worsen cerebral edema, multiple brain metastases are usually treated with whole brain RT. But for solitary brain lesions, Surgery or SRS are used. For up to four brain metastases, surgical excision combined with SRS or SRS alone may be explored [18,19].

Recent Guidelines

The ATA Guidelines 2015 recommend against routine adjuvant EBRT to the neck after R0 resection but suggest RAI combined with EBRT for R2 resections [4]. The American Head and Neck Society advises EBRT for individuals over 45 with limited RAI-avid gross disease but not for cervical lymph node involvement alone [20].

The British Thyroid Association suggests EBRT for significant residual and recurrent disease when further surgery or radioiodine is ineffective [11].

Role of RT in medullary and anaplastic thyroid cancer

Medullary thyroid cancer

Routine EBRT has not been shown to increase survival in medullary thyroid cancers and should only be considered after optimal surgery if there is a high risk of local recurrence or macroscopic residual disease. Palliative radiation can be beneficial for painful bone metastases and unresectable masses [21].

Anaplastic thyroid cancer

Anaplastic thyroid carcinoma is uncommon and has an aggressive clinical course, making it challenging to conduct clinical trials and establish high-quality evidence on which to base practice.

Recent ATA guidelines recommend adjuvant radical EBRT for patients with R0/R1 resection, excellent performance status, and no distant metastases. EBRT is also suggested for unresectable tumors, with reassessment for surgical resection post-EBRT [22].

Radiotherapy-pretreatment evaluation, technique, dose, and volumes

Following dental, speech, swallowing, and nutritional evaluations, target volumes are delineated using available pre-treatment contrast-enhanced computed tomography, magnetic resonance imaging, positron emission tomography-computed tomography, and whole-body iodine scans. Any gross residual disease, the thyroid bed, including the trachea-esophageal grove, and draining lymph nodes (pre-tracheal, paratracheal, cervical, and superior mediastinal lymph nodes) should be included in the target volumes.

In DTC, intensity-modulated radiation therapy is the preferred approach for delivering RT. The literature contains a wide range of dosage regimens. The most common EBRT doses are: 66-70 Gy for gross residual or unresectable disease, 60-66 Gy for microscopic disease, thyroid bed and positive nodes, and 50-56 Gy for elective nodal areas [14,23,24].

Radiotherapy toxicities

Acute RT side effects include skin erythema, desquamation, mucositis, and dysphagia, while late complications include esophageal and tracheal stenosis, chronic dysphagia, and feeding tube dependency. A multicenter study found that most patients exhibited grade 0-2 acute toxicities, with 9% experiencing acute grade 3 skin erythema. No late grade 3 toxicities were observed [25].

Conclusion

Thyroid cancer is a curable disease with highly effective targeted therapy available. However, radiation therapy has a role in certain situations, and all patients should be discussed in multidisciplinary meetings before making informed decisions.

List of Abbreviations

ATA	American thyroid association
R0	Complete resection with negative margins
R1	Microscopic positive margins
R2	Gross positive margins and residual disease
TSH	Thyroid stimulating hormone

Consent to participate

Yes all consented to participate.

Ethical approval

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