Research Article

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Role of External Beam Radiotherapy in Thyroid Cancer

Xavier Fernando Cardenas Chavez[1]*, Carlos Jose Caballero Hernandez[2], Cindy Paola Cerro Martinez[3], José Fernando Villalba Garcia[4], Juan Carlos Peralta Farak[4], Andrea Carolina Contreras Castro[4], Karenth Yuliana Hurtado Soler[5], Mario Alberto Chadid Silgado[6], José Mario Porto Corbacho[7], Mayra Susana Gomez Lizarazo[8]

[1]*General doctor, Universida del Sinú, Colombia, https://orcid.org/0000-0002-8069-8191*

[2]*General doctor, Universidad del Norte, Colombia, https://orcid.org/0000-0001-9304-865X*

[3]*Gynecologist, Universidad Libre, Colombia, https://orcid.org/0000-0001-9915-1789*

[4]*General doctor, Corporación Universitaria Rafael Núñez, Colombia; https://orcid.org/0000-0003-0286-2563; https://orcid.org/0000-0001-5337-1364; https://orcid.org/0000-0003-2027-5442*

[5]*General doctor, Universidad Sur colombiana, Colombia; https://orcid.org/0000-0001-5038-0388*

[6]*General doctor, Universidad de Sucre, Colombia, https://orcid.org/0000-0002-9343-8030*

[7]*General doctor, Fundación universitaria de ciencias de la salud (FUCS); https: //orcid.org/0000-0002-6685-790X*

[8]*General doctor, Universidad de Santander UDES, Colombia; https://orcid.org/0000-0001-6252-3067*

ABSTRACT

Background: Radiotherapy is the use of targeted X-rays or subatomic particles primarily for the treatment of cancer in curative and palliative settings. It can be delivered either externally or internally. The therapeutic window on radiation is also based on differences in DNA interactions in a cancer cell versus a normal cell. External beam radiotherapy, in differentiated thyroid cancer, it is known that there is little information about it, it is known that there is a lack of prospective clinical data.

Methodology: A systematic review was carried out through various databases from January 2014 to February 2023; The search and selection of articles was carried out in indexed journals in English.

Results: One of the objectives of external beam radiotherapy in differentiated thyroid cancer is to optimize locoregional control and limit the toxicity of the treatment. The intensity of external beam radiotherapy can be definitive, adjuvant, or palliative. There are many risk factors for recurrence or locoregional progression in thyroid cancer. This method can be used in gross or unresectable residual disease.

Conclusion: This review offers up-to-date and detailed information on the essential role played by external beam radiotherapy in the different types of thyroid cancer.

KEYWORDS: Radiotherapy; Cancer; Thyroid; Residual disease

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Address for correspondence: Xavier Fernando Cardenas Chavez, General physician, Universida del Sinú, Colombia, https://orcid.org/0000-0002-8069-8191

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INTRODUCTION

Radiotherapy is the use of targeted X-rays or subatomic particles primarily for the treatment of cancer in curative and palliative settings. It can be delivered either externally or internally. External beam radiation, also known as "teletherapy", is the most common and involves a radioactive source outside the patient, with the energy focused and tailored to the target of interest [1,2]. Brachytherapy, by contrast, refers to the practice of placing naturally occurring radioactive sources that decay over time and produce high doses of radiation in a focal area [3].

The most common form of ionizing radiation used in clinical practice is the photon. However, electrons are also commonly used to increase the radiation dose to the skin when necessary. More exotic particles such as protons, carbon ions, or neutrons can be used for certain diagnoses or tumor locations. Each type of radiation has unique physical characteristics that dictate the type of interactions that will occur as it travels through the patient's body. This, in turn, determines how and where the dose is deposited in the tissue [4]. The therapeutic window on radiation is also based on differences in DNA interactions in a cancer cell versus a normal cell. Double-stranded DNA breaks caused by radiation result in mitotic catastrophe in which cell division is fatally interrupted; Mitotic catastrophe is the main form of cell death induced by ionizing radiation [5].

Therefore, the radiosensitivity of a cell line depends on its rate of cell division. In general, poorly differentiated tumor cells are more radiosensitive because a greater proportion of their cell population is dividing at any given time. This also applies to normal, rapidly dividing tissue cells, such as those of the gastrointestinal mucosa, and explains why reactions such as mucositis and diarrhea can be common [6]. The dependence of the effect of radiation on the phase of the cell cycle is the basis of one of the four basic principles of radiation biology that dictate the success of a particular regimen: the redistribution of cells within the cycle. cell, DNA damage repair, the repopulation of cells and the repopulation or oxygenation of hypoxic areas within the tumor [7].

Radiation takes advantage of cancer cells because these cells generally have damaged DNA repair mechanisms, in contrast to normal cells, which can quickly repair double-strand breaks. Therefore, a fractional approach is typically used, that is, dividing the total radiation dose into several daily treatments, so that DNA damage in normal cells is repaired between treatments, while damage in cancer cells accumulates over time, causing preferential cell death [8]. Both the fractional dose and the total dose affect the response of the tumor and normal tissue. In general, the lower the daily dose of radiation, the less likely it is to cause toxicity, but only specific cell lines (such as myeloma or lymphoma) are susceptible to these relatively low daily doses [9]. In this work we will base ourselves on the role of external beam radiotherapy in differentiated thyroid cancer, since there is little information in this regard, it is known that there is a lack of prospective clinical data, as well as the lack of homogeneity and the Conflicting results in existing retrospective data [10].

Studies have reported that there is a growing number of retrospective studies, including several recent studies showing significant benefit for external beam radiation therapy in selected patients. As is the case with differentiated thyroid cancer, since it presents good locoregional control as well as limiting the toxicity of the treatment [11]. For most patients with differentiated thyroid cancer, surgery and radioactive iodine are effective in achieving locoregional control. However, in cases where surgery or radioactive iodine is less effective, External Beam Radiotherapy may be recommended. Intent to treat this is generally classified as definitive (for curative treatment of gross disease), adjuvant (for treatment of presumed residual disease after surgery), or palliative (for symptom control). However, in differentiated thyroid cancer, these categories are often blurred, as patients with unresectable disease or distant metastases may still have a fair overall prognosis and may suffer the consequences of uncontrolled disease in the central part of the neck [12]. Therefore, it is necessary to carry out this work in order to provide updated and detailed information on the role of external radiotherapy in thyroid cancer.

MATERIALS AND METHODS

A systematic review was carried out, the databases that were implemented are: PubMed, Scielo and ScienceDirect, among others. Articles from indexed journals in English from the years 2014 to 2023 were collected and selected. As keywords, the terms were taken into account: Radiotherapy; Cancer; Thyroid; Residual disease. In this review, 86 original and review publications related to the subject studied were identified, of which 31 articles met the specified inclusion requirements, such as articles that were in a range of not less than the year 2014, that were articles from full text and inform about the subject. As exclusion criteria, it was taken into account that the articles did not have sufficient information and that they did not present the full text at the time of their review.

RESULTS

External Beam Radiation Therapy

This is a topic of great importance and to date with little prospective clinical data demonstrating its efficacy, importance and safety. It is optimally used in a small subset of thyroid cancer patients with aggressive locoregional disease [12,13]. One of the objectives of external beam radiotherapy in differentiated thyroid cancer is to optimize locoregional control and limit the toxicity of the treatment. To date surgical interventions and radioactive iodine are considered effective. But not all patients have the same positive and therapeutic results, so external beam radiotherapy should be recommended in these cases [13]. In Table 1, we can identify the intention of treatment with external beam radiotherapy [13-16]. For patients with distant metastases, the importance of locoregional control must be weighed against the overall prognosis and potential toxicities of external beam radiation therapy. For example, some patients with radioactive iodine-avid lung metastases and unresectable or residual neck disease may be recommended external-beam radiation therapy to the neck with a dose of 60 to 70 Gy, while other patients with non-avid uncontrolled lung metastases of radioactive iodine and symptomatic neck disease may be recommended palliative treatment, external beam radiation therapy of the neck with lower doses. In Figure 1, we can identify the main risks of recurrence or locoregional progression in thyroid cancer [17-20].

Gross or Unresectable Residual Disease

For patients who meet this criteria, external-beam radiation therapy is recommended for patients with unresectable or residual gross locoregional disease, except for patients <45 years with limited gross disease who are avid for radioactive iodine [21]. Locally invasive thyroid cancer can affect the strap muscles, recurrent laryngeal nerve, trachea, larynx, esophagus, or major vessels. With careful preoperative planning and evaluation, most cases of invasive disease can be resected without gross residual disease, but there will inevitably be some cases of unresectable disease or gross residual disease that cannot be treated with further resection. This most often occurs in the context of recurrent disease. In addition, there are also some patients who do not wish to undergo aggressive function-sacrificing aerodigestive tract surgery or who have medical comorbidities that make surgery inadvisable. In these patients, it is important to decide the intention of treatment in advance (definitive or palliative), since the probability of locoregional control with external beam radiation therapy is dose related, but toxicities also increase with dose. It has been confirmed, through many retrospective studies, which show long-term locoregional control with the use of external beam radiotherapy in patients with unresectable or macroscopic residual differentiated thyroid cancer [22].

Table 1: Classification of external beam radiotherapy.

Classification	Synthesis
Final	For the curative treatment of gross disease
Adjuvant	For the treatment of presumed residual disease after surgery
Palliative	For symptom control

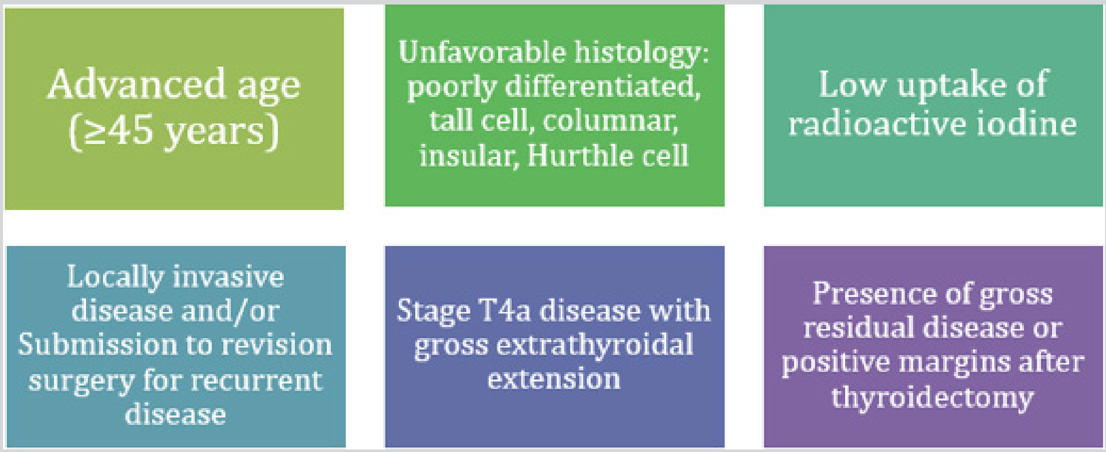

Figure 1: Risk factors for recurrence or locoregional progression in thyroid cancer.

Microscopic Residual Disease after Complete Resection

In these patients, external beam radiotherapy should not be used routinely as adjuvant therapy after complete resection of gross disease. The use of adjuvant external beam radiotherapy after complete resection of invasive differentiated thyroid cancer is highly debated, with no routine indications and differing opinions and practices at different institutions. For each patient, there are multiple surgical and pathologic factors that contribute to the risk of microscopic residual disease, and there are several treatment options that affect long-term locoregional control, including radioactive iodine, external beam radiation therapy, and additional surgery.

Invasive thyroid cancer can affect the strap muscles, the recurrent laryngeal nerve, or the trachea; less commonly, it may involve the larynx, esophagus, or major vessels. Although most cases of invasive disease can be excised without gross residual disease, a significant number will have microscopic residual disease. In general, tumors with anterior extension to the strap muscles are considered respectable with minimal morbidity and without the need for reconstruction. Posteriorly spreading tumors may be more challenging. The recurrent laryngeal nerve (RLN) can be sacrificed if it is covered by a tumor and there is preoperative ipsilateral vocal cord paresis. However, if there is ipsilateral function, the tumor can be shaved to preserve the recurrent laryngeal nerve as long as all gross disease is removed; in this case, there is a risk of microscopic residual disease [23].

If a short segment of the trachea is involved with minimal cartilage invasion, a shaved tracheal excision is considered appropriate, but circumferential sleeve resection may be indicated for more significant cartilage invasion or intraluminal invasion. In cases where the jugular vein is affected by extensive nodal extracapsular spread, the vein can be excised without reconstruction when the contralateral vein is patent, but again there may be a risk of microscopic disease in the neck [24]. Regarding the use of radioactive iodine in differentiated thyroid cancer, thyroid epithelial cells and well-differentiated thyroid cancer cells take up iodine, thus 131I beta emitter is an effective targeted radiopharmaceutical for differentiated thyroid cancer. . Radioactive iodine therapy can be used after primary surgery for ablation of the normal thyroid remnant as adjunctive therapy for risk of microscopic disease [25].

Adjuvant External Beam Radiation Therapy

After complete resection, external beam radiation therapy may be considered in selected patients older than 45 years with a high probability of microscopic residual disease and a low probability of responding to radioactive iodine. This scenario can occur in the setting of gross extra-thyroid extension or with revision surgery for persistent or recurrent disease. In patients with cervical lymph node involvement alone, this should not be an indication for adjuvant external beam radiotherapy. After complete resection of differentiated thyroid cancer, patients with cervical node metastases are at risk for microscopic residual nodal disease. However, as noted above, adjuvant radioactive iodine is usually quite effective in eliminating microscopic residual disease in the nodes [26]. Recurrences of differentiated thyroid cancer in the nodes are more easily saved (with neck dissection) than recurrences in the thyroid bed. Therefore, after complete resection, cervical lymph node involvement alone should not be an indication for EBRT, but may be considered if there is extensive extracapsular spread with high risk of microscopic residual disease. . In Table 2 we can find the recommended doses according to the state in which the patient is [27-29].

Table 2: Dose of external beam radiotherapy depends on the state or risk of metastasis.

Radiation Therapy Dose	Status or Risk of Metastasis
70gy	Gross disease
66Gy	Areas of positive surgical margin or shave excision
60gy	Areas at high risk of microscopic disease (including the thyroid bed, tracheoesophageal groove, and level VI cervical nodes)
54Gy	Areas with low risk of microscopic disease (including uninvolved level II-V and VII lymph nodes)

DISCUSSION

This is a topic of great importance and to date with little prospective clinical data demonstrating its efficacy, importance and safety. One of the objectives of external beam radiotherapy in differentiated thyroid cancer is to optimize locoregional control and limit the toxicity of the treatment. The study by Sarah [30] in which they conduct an exploratory review of the use of external beam radiotherapy in well-differentiated thyroid cancer, in which they review the published literature on External Beam Radiotherapy for advanced pT4 disease and gross unresectable disease to improve locoregional control. Further discussing the use of radiotherapy for patients with metastatic disease. Concluding that external beam radiotherapy is indicated and has good evidence in the context of unresectable gross residual well-differentiated thyroid cancer, as this may result in long-term local control. Although the evidence on the benefit of radiotherapy in patients with locally advanced disease that is completely resected is still not entirely conclusive.

Another study carried out by Salem [31] reports that external beam radiotherapy in differentiated Thyroid Cancer is not a well-established treatment modality, since the data are limited to small retrospective studies. Although they report that most series have shown an increase in locoregional control. Therefore, external beam radiotherapy should be reserved for patients at high risk of locoregional recurrence, and clinicians are urged to consider the potential benefits and potential toxicity. These studies demonstrate the efficacy and great therapeutic effect of external beam radiotherapy in certain types of thyroid cancer, so its use in clinical practice is considered safe, since it is necessary to identify the type of thyroid cancer that the patient presents. to be able to implement this radiotherapy. A strength of the current study is the methodology implemented, regarding the literature search, and steps in the selection of relevant articles, quality assessment, and data extraction. However, we still need more studies and therapeutic approaches to be able to completely eradicate locally advanced disease in most patients, since there are not enough studies that demonstrate its correct diagnostic and therapeutic approach, so more studies are needed to answer these questions.

CONCLUSION

One of the objectives of external beam radiotherapy in differentiated thyroid cancer is to optimize locoregional control and limit the toxicity of the treatment. For patients with distant metastases, the importance of locoregional control must be weighed against the overall prognosis and potential toxicities of external beam radiation therapy. There are many risk factors involved, among which we highlight advanced age, unfavorable histology, low uptake of radioactive iodine, among others, as shown in Figure 1. It must be taken into account that after complete resection of differentiated thyroid cancer, patients with cervical node metastases are at risk for microscopic residual nodal disease. Therefore, radioactive iodine is of great importance in this regard.

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