Review Article

Review Article in Poorly Differentiated Cancer Thyroid, An overview.

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Abstract
Worldwide, the incidence of thyroid cancer has greatly increased in the last decades with female predominance. Increase in incidence of more advanced disease has also been reported. Poorly differentiated thyroid cancer is a rare aggressive subtype of thyroid cancer that does not appear de-novo from the start, it starts as differentiated cancer then dedifferentiation occurs by genetic factors. It is the main cause of death from non-anaplastic follicular cell derived thyroid cancer. It expresses thyroglobulin, as differentiated thyroid cancers and usually does not concentrate radioactive iodine with increased glucose transporter 1 expression, like anaplastic thyroid cancers. This type of cancer has high risk of local recurrence and distant metastasis. Management of this type of cancer is challenging with overall poor therapy response and prognosis with high mortality rate when compared to differentiated thyroid cancers. Surgery is the standard management in early operable cases followed by radioactive iodine therapy (after testing avidity)/radiotherapy/chemotherapy and the recently available molecular targeted therapies are promising.
Key Words: Poorly differentiated thyroid cancer; incidence; prognosis; management; chemotherapy; radioactive iodine; PET/CT.

Introduction
Poorly differentiated thyroid cancer (PDTC) is a category of thyroid malignancies that falls between differentiated and anaplastic thyroid cancers with more aggressive pattern than the classic differentiated type and not yet reaching the level of aggressiveness of the anaplastic type[(1)]**.** It is a rare type of cancer that represents less than 6% of all thyroid cancers with poor prognosis and in 50% of cases, it is presented with nodal and/or distant metastasis[(2)].

Diagnosis:
Pre-operative fine needle aspiration cytology and postoperative histopathological examination are diagnostic. Macroscopically, the tumor is solid, greyish-white with necrotic foci and marginal invasion. Microscopically, the diagnosis depends mainly on the presence of non-glandular tissues. The tumor consists mainly of solid clusters with variable amount of follicles [(3)].

Prognosis:
PDTC has aggressive course with poor outcome. It often displays extensive local, lymphatic and distant metastasis (lung and bone)[(4)]. One third of all patients develop recurrence and a small percent of patients with distant metastatic disease may achieve remission on radioactive iodine therapy[(5)].

Treatment:
Management of PDTC challenging and controversial

1- Surgery: Due to the aggressiveness of this type of tumor, surgical excision with total thyroidectomy is the main therapeutic procedure and due to high incidence of nodal metastasis, nodal dissection is usually needed[(6)].
2- Radioactive Iodine therapy (RAI): PDTC originates from follicular cells

of thyroid gland. So, most preliminary studies showed that some of them still retain the ability of concentrating radioactive iodine and secreting thyroglobulin[7].

3- External beam radiotherapy (EBRT): It is used as a local control of the disease and to reduce the incidence of local recurrence with no impact on overall survival. EBRT can represent a valuable treatment tool in unresectable, incompletely resected tumors and in loco-regional recurrence[8].

4- Chemotherapy (CTH): in non-iodine avid and iodine avid non-responding PDTH, CTH could by an available option for treatment either alone or in combination with EBRT. Doxorubicin, Platins and taxans are the most effect-tive agents in thyroid cancers with overall inadequate therapy outcome[9].

5- Molecular therapy: as tyrosine kinase inhibitors (TKIs) which are oral multi-targeted drugs that disrupt the angiogenesis process in the tumor hence affecting its blood supply and growth. They are used in advanced iodine-resistant thyroid tumors with promising results, however, their availability and expenses are major limiting factors of their use[10].

Follow up:

Due to aggressiveness of the disease and high liability of recurrence, patients must be kept on close surveillance. Serum thyroglobulin assessment, neck ultrasonography, iodine imaging, CT, MRI and FDG PET/CT are available tools for assessment[11].

Role of PET/CT in poorly differentiated cancer thyroid:

Although PET/CT has a limited role in well-differentiated thyroid cancer management and is almost restricted to thyroglobulin elevated negative iodine scan (TENIS) cases, in PDTC the increased glucose demand by rapidly proliferating cells with up regulation of glucose transporter 1 makes PET/CT very helpful in assessment of this type of thyroid cancer with high FDG uptake[12] PET/CT scan is preferred rather than radioactive iodine scan in assessment of all stages of PDTC due to its higher sensitivity and specificity with inverse relation noted between tumor activity (SUV max) and survival in initial assessment of the tumor[13].

Conclusion

Management of poorly differentiated cancer thyroid is challenging. In most cases, it is radioactive iodine resistant. RTH can reduce incidence of local recurrence. CTH is an available option. Newly developing target therapy is the current hope, limited by availability and expense. PET/CT has a major role in staging and assessment of response to therapy and follow up of non-iodine avid lesions.

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