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CASE REPORT

SMALL CELL NEUROENDOCRINE THYROID CARCINOMA

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Abstract. Extrapulmonary small cell neuroendocrine carcinomas are defined by the presence of the small cell cancer in the absence of any evidence of primary lung cancer. We present the case of a 51 years old female that was diagnosed with primary thyroid small cell neuroendocrine carcinoma. After thyroid biopsy was performed, the histological and IHC profiles revealed a small cell neuroendocrine tumor with, with positive reaction to synaptophysin, chromogranin, cytokeratin 7. The negative reaction to TTF-1, thyroglobulin, calcitonin and further investigations (PET-CT, brain MRI, bronchoscopy) exclude primary lung carcinoma, thyroid carcinoma (differentiated or medullary types) and distant metastasis. After 6 Cisplatin-Etoposide cycles, poor disease response was found. Radiotherapy was performed with favourable results. The team managing the case chose to follow the guidelines for primary thyroid carcinoma in delineating the treatment volumes and the small cell lung cancer guidelines for dose and fractionation schedule. Due to its rarity, primary thyroid small cell neuroendocrine carcinoma poses a challenge for physicians because there are no set guidelines for the management of this disease.
Keywords: small cell neuroendocrine, carcinoma, thyroid, radiotherapy.

Introduction

Extrapulmonary small cell carcinomas (ESCCs) were first described by Duguyd and Kennedy in 1930 [1]. These are extremely rare types of tumors, representing 2.5-4% of all small cell carcinomas [2,3]. ESCCs can be defined by the presence of a small cell cancer in the absence of any evidence lung primary, with normal CT or PET-CT, normal bronchoscopy and sputum cytology.

Most frequently ESCCs were found in the urinary bladder, prostate, oesophagus, stomach, colon and rectum, gallbladder, larynx, salivary glands, cervix, skin [4,5,6,7]. Small cell carcinoma will occasionally present with metastatic disease, and the primary site cannot be identified -small cell carcinoma of unknown primary [8,9].

ESCCs are part of the neuroendocrine family of tumours and could originate from multipotential stem cell cells with the capability of divergent differentiation [9,10].

ESCCs immunophenotypes have both epithelial and neuroendocrine features with positive stains for the common neuroendocrine markers like synaptophysin and chromogranin-A, but also for general epithelial markers such as keratin [10].

The differential diagnosis should include: metastatic small cell lung cancer (SCLC), other types of neuroendocrine or carcinoid tumors, other types of carcinomas[11].

The most used staging is the two-stage classification used for SCLC, the limited-stage representing diseases confined to the primary site and adjacent organs (which can be encompassed within a tolerable radiation therapy port) and the extensive-stage is beyond the limited-stage [12].

Because of its rarity there are no standard guidelines for the management of ESCCs. Most of the authors recommend following the SCLC guidelines. For limited-stage diseases, surgery is an option, in contrast to SCLC. There are still controversies regarding the multimodality treatments using chemotherapy and radiotherapy. For extensive-disease, chemotherapy seems to play the most important role.[11,13,14,15].

Patient, Methods and Results

We present a case of a 51 years old female with a history of smoking 1 pack/day for 15 years, family history N/A. In October 2013, difficult swelling started on the right side of the neck, followed in January 2014, by shortness of breath. Tracheostomy was opened in Jan 2014 due to acute respiratory failure; biopsy from right thyroid lobe was obtained.

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Further investigations showed: brain MRI within normal limits, bronchoscopy – external compression to subglottis trachea, FT 4, TSH, Calcitonin within normal limits, PET-CT: abnormally increased metabolic activities observed within multiple masses occupying thyroid gland location, anterior aspect of the larynx and left side of the neck, no other significant changes compatible with malignant tissue.

The pathology and immunohistochemistry reported small atypical cells with hyperchromatic nuclei and diffuse necrosis. Synaptophysin, Chromogranin, Cytokeratin 7 where positive and TTF-1, thyroglobulin, CD45 and calcitonin negative, with Ki-67 proliferation index at about 80%.

No evidence of primary lung on PET-CT and bronchoscopy exclude SCLC and the negative reaction for thyroglobulin and calcitonin exclude the thyroid differentiated or medullary types of carcinoma.

Histomorphological, immunohistochemical, clinical and imaging features are compatible with a small cell neuroendocrine thyroid carcinoma, limited stage.

Chemotherapy was planned with Radiotherapy re-evaluation after the completion of the systemic treatment. 6 Cisplatin-Etoposide cycles were completed with no favourable results. CT after chemotherapy showed persistent masses in the thyroid gland, involving proximal trachea with no regional lymphadenopathy and no evidence of pulmonary tumours. We submitted the case to the head and neck tumour board and radiotherapy was recommended.

We started 3D conformal radiotherapy with CT planning, using also pre chemotherapy PET-CT data. For positioning and immobilization the patient was supine with neck extended, with the use of an aquaplast mask to immobilize head and shoulders. CT scan was performed with i.v. contrast, 3 mm thick slices, from base of skull to carina. For treatment volume delineation and planning we used an Eclipse treatment planning system.

According to ICRU recommendations and thyroid carcinoma external beam radiotherapy protocols, CTV_44 included uninvolved bilateral cervical nodes, levels II–IV, VI and superior mediastinal nodes (fig. 1).

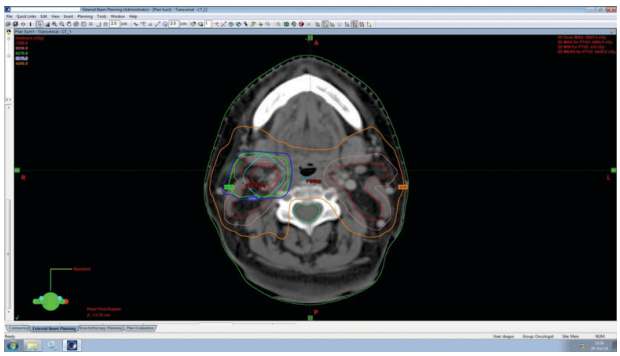

Figure 1. CT axial slice showing CTV-44 (red) and CTV_66 –nodal (cyan).

CTV_66 included the GTV tumoral (fig.2) and nodal (fig1.) as seen on planning CT and pre chemotherapy PET-CT.

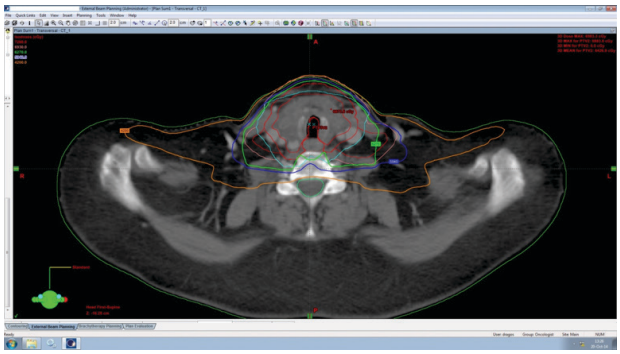

Figure 2. CT axial slice showing CTV_66 tumoral (red)

We used multiple coplanar photon beams for achieving a good dose distribution (fig. 3). The dose/ fractionation schedule was 2Gy/ fraction, 1 fraction/ day, 5 days/ week, 44 Gy in 22 fractions for CTV_44 and 66 Gy in 33 fractions for CTV_66

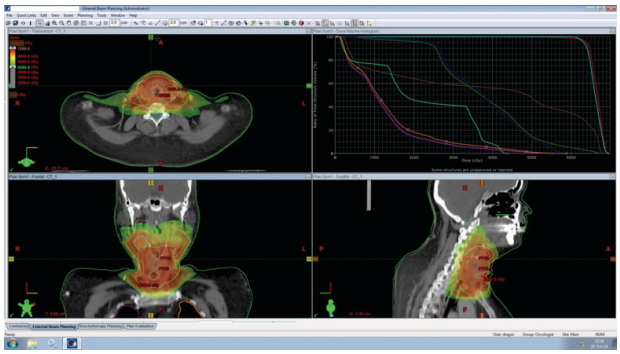

Figure 3. Dose distribution (color wash) and dose volume histograms

For treatment delivery we used a Varian Clinac iX linear accelerator, with multiple 6 MV photons beams. Verification was performed with OBI kv imaging system, with images taken on days 1-3 and then weekly.

During treatment the patient experienced acute side effects: grade 2 esophagitis, grade 2 dermatitis, grade 1 anaemia, grade 1 neutropenia and grade 1 weight loss. Supportive active care was provided.

The follow-up 4 weeks after radiotherapy completion found no clinical evidence of tumour, blood work within normal limits. Further recommendations consist in: imaging at 8 weeks post-radiotherapy, physical examinations every 3 months for the first 2 years, every 6 months for years 3-5, then annually. If the treatment proves to be optimal, there should be an evaluation regarding the opportunity of the prophylactic cranial irradiation in this case.

Discussion

Extrapulmonary small cell carcinoma is usually treated similarly to small cell lung cancer. Differences in aetiology, clinical course, frequency of brain metastases, and survival, however, warrant a differential therapeutic approach [16].

For this case we chose to follow the guidelines for primary thyroid carcinoma in delineating the treatment volumes and the small cell lung cancer guidelines

for dose and fractionation schedule. Concurrent chemoradiation, altered fractionations are valid options for similar cases. One particular feature in this case is the unsatisfactory response to chemotherapy.

There is a controversy regarding the use of prophylactic cranial irradiation in ESCCs after completion of the optimal treatment, because of the lower incidence of brain metastasis as compared with pulmonary small cell carcinoma. An exception is ESCCs originating from the head and neck region which are associated with a higher incidence of brain metastasis, justifying addition of PCI [16].

Conclusion

Due to their rarity, primary thyroid small cell neuroendocrine carcinomas pose a challenge for physicians, regarding diagnosis and treatment. Although there are no set guidelines for the management of the ESCCs prospective trials are warranted.

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