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Primary squamous cell carcinoma of the thyroid: Case report and systematic review of the literature



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ABSTRACT

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Keywords: Primary squamous cell cancer Thyroid Surgery Radiochemotherapy Case report Systematic review *BACKGROUND:* Primary squamous cell cancer (PSCC) of thyroid is a rare malignancy with poor prognosis. It is mandatory to exclude secondary involvement of the thyroid by panendoscopy, CT-scan and immunohistochemical analysis. As treatment surgery, radiation and rarely chemotherapy is employed. *METHODS:* A systematic review of the literature was conducted searching medline and embase database using the medical subject headings "primary squamous cell carcinoma of thyroid" and "primary squamous cell cancer of thyroid", for articles published until April 2016 (n = 1733). Of interest were the used treatment modalities and survival outcomes.

RESULTS: A total of 35 publications reporting on 50 cases including ours were finally analyzed. A curative treatment approach was described in 24 patients (48%). Additional radiotherapy, chemotherapy or radiochemotherapy was applied in 17, 7 and 7 patients respectively. Median overall survival was 6 months [range 0–48] for 47 patients. Disease free survival was only achieved in 8 patients with disease limited to the thyroid gland, complete surgical resection and additional radiotherapy or radiochemotherapy [reported median 20 months; range 12–48].

CONCLUSION: Reported disease free survival of PSCC of the thyroid was only achieved in patients with complete surgical resection in combination with adjuvant radio- and/or chemotherapy. However long term survival has not been reported in the literature yet.

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1. Introduction

Primary squamous cell carcinoma (PSCC) of the thyroid is a rare neoplasm and constitutes less than one per cent of all primary thyroid carcinomas [1]. It can occur at any age but the median age of presentation is the fifth and sixth decade [2]. It is usually diagnosed as advanced disease with infiltration in adjacent organs or as an incidentaloma with poor prognosis. It is crucial to exclude any metastatic disease, direct extension from an extra-thyroidal primary tumor and the association with a tall cell variant of papillary carcinoma of the thyroid before making the diagnosis as this has impact on potential treatment [3]. Therefore mandatory tools for the diagnosis of primary squamous cell carcinoma of the thyroid are panendoscopy, CT-Scan or PET-CT and immunohistological analysis [4]. The ideal potentially curative treatment has not been ruled out yet. Currently, there are different treatment option described which include surgery, chemotherapy and radiation [5]. Additionally, the value of lymphadenectomy has not been further investigated for the patientís outcome.

2. Methods

The following case report was presented according to the SCARE guidelines [6]. Additionally a systematic review of the literature was conducted searching medline and embase database using the medical subject headings "primary squamous cell carcinoma of thyroid" and "primary squamous cell cancer of thyroid", for articles published until March 2016. All English written publications reporting on primary squamous cell carcinoma of the thyroid were included. Complete diagnostic work up including immuno-histochemistry, CT-Scan and panendoscopy to exclude secondary squamous cell cancer of the thyroid were also included by the diagnosis of an autopsy study, which showed no other source of squamous cell carcinoma than the thyroid. We excluded following cases:

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- · cases of secondary disease to the thyroid
- cases which have been diagnosed only by fine needle aspiration cytology (FNAC)

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- cases in which SCC was present in association with other thyroid malignancies
- such as papillary carcinoma, adenocarcinoma or anaplastic carcinoma
- cases in which complete diagnostic work-up as CT-scan, panendoscopy and immunohistochemistry was not performed
- double citations

The objectives of this review were the evaluation of the assessment of local and distant tumor extension, described treatment options (surgery, radiotherapy, chemotherapy), number of patients with curative intended treatment and the outcome parameters recurrence, disease free and overall survival with respect to additional radiotherapy and/or chemotherapy. A curative intended treatment was assumed when a complete (R0) resection was achieved.

3. Case presentation

3.1. Patient history and treatment

A 61- year old female patient with the history of a hashimoto thyreoiditis was admitted at our hospital because of a clinically visible single thyroid nodule in the left lobe. Cervical sonography revealed a total thyroid volume of 11.7 ml with a single hypoechogenic nodule of $2.5 \times 2.1 \times 2.4$ cm, displaying an irregular ventral contour. A scintigraphy showed the nodule to be hypofunctional. Additionally the patient had diagnosed a non-classified collagenosis with fibrosis of the lung. The operation was initiated as a hemithyreoidectomy left. After the diagnosis of a squamous cell carcinoma in the frozen section biopsy the operation was completed as a total thyroidectomy. Because of sonographic unsuspicious cervical lymph nodes a prophylactic lymphadenectomy was not performed. The postoperative course was uneventful and the patient could be discharged at the 3rd postoperative day. The possibility of secondary thyroid involvement deriving from other primary cancers was ruled out by PET-CT and panendoscopy. Postoperatively the patient received 30 fractions of adjuvant radiation therapy of the thyroid bed, the regional lymphatic drainage and the mediastinum with 54 Gy and a boost of the thyroid bed with 60 Gy over a 8-week period. 37 months after surgery, the patient developed a local recurrence infiltrating the left carotic artery and pulmonary metastasis. The patient refused any further treatment but is still alive 40 month after initial surgery.

3.2. Histopathological and immunohistochemical findings

The resected thyroid weighed 15 g. The left thyroid measured $4,0 \times 3,0 \times 2,2$ cm. The cut surface showed a withish tumor with a size of $2,7 \times 2,0 \times 1,5$ cm and the margins were clean. The right thyroid weighed 5 g with a size of $3,5 \times 2,5 \times 1,9$ cm and an unremarkable cut surface. Microscopically the tumor appeared as a knotty grown solid epithelial neoplasm with

herd-like necrosis and hyperchromatic nuclei with prominent eosinophilic nucleoli, partially with horn formation. The tumor cell complexes were surrounded by collagen-rich connective tissue, with patch shaped lymphocytic infiltrates, which partially formed secondary follicles.

Histopathology and immunohistochemistry showing positivity for p63, CK5 is displayed in Fig. 1a–c while staining for thyroglobulin was restricted to the non-neoplastic thyroid tissue (Fig. 1d). In summary, the specimen showed a 2,7 cm in size, low differentiated, keratinizing squamous cell carcinoma. The surrounding parenchyma was presenting with a lymphocytic thyroiditis, presenting a final TNM-classification: pT2, pNx, L0, V0, G3, R0



Fig. 1. a) Hematoxylin and eosin $-staining 200\times$, b) Cytokeratin 5/6 immunohistopathology, c) p63 immunohistopathology, d) thyroglobulin immunohistopathology.

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Fig. 2. The flow chart of identified studies.

4. Results of systematic literature review

1733 abstracts could be extracted from medline and embase database using the medical subject headings "primary squamous cell carcer of thyroid". A flow diagram of literature research is displayed in Fig. 2. According to the inclusion/exclusion criteria, 52 full papers with reporting of 97 cases were screened. Some 17 publications with 48 cases without complete work-up, including CT-scan, panendoscopy, immunohistochemistry and double citations were excluded [6–22]. Finally, 35 papers and ours reporting on 50 patients were available for analysis [2–523–53].

The median age of these 50 patients was 64 years [range 28–88] with a higher prevalence in woman (n = 35; 70%). Patient characteristics and treatment details are listed in Table 1. Patients were grouped into cases with curative treatment intention (complete surgical resection) and palliative treatment intention (incomplete surgical resection). A coexisting Hashimoto thyroiditis was described in eight cases. Locally advanced tumor stage was described in 43 patients (86%), 26 patients (52%) had tumor infiltrated cervical lymph nodes and 5 patients (10%) had distant metastasis at the time of diagnosis. Complete resection of the tumor was achieved in 24 patients (48%) and thus a curative treatment approach was assumed.

As surgical treatment 30 patients had a total thyroidectomy (60%) whereas 10 patients had a hemithyreoidectomy (20%) and 10 subtotal thyroid resection (10%). 27 patients (54%) had an additional cervical lymphadenectomy.

Table 1

Patient characteristics and treatment details.

	Curative treatment intention n=	Palliative treatment intention n=
Patients	24	26
Median Age in years [range]	60 [28-88]	66 [36-82]
Female	17	18
Coexsiting Hashimoto thyroiditis	5	3
Staging		
T1/2	5	2
T3	11	1
T4	8	23
N+	11	15
N-	12	4
N-Status not mentioned	1	7
M+	0	5
M-	23	19
M-Status not mentioned	1	2
G1	2	2
G2	1	4
G3	7	6
G-Status not mentioned	14	14
Surgery		
Thyroidectomy	16	14
Hemithyroidectomy	8	2
Other subtotal thyroid resection	0	10
additional Lymphadenectomy	19	8
Additional Treatment		
Preoperative Chemotherapy	1	0
Postoperative Radiotherapy	10	7
Postoperative Chemotherapy	4	2
Postoperative Radiochemotherapy	3	4

Regarding a postoperative additional treatment, 17 patients received a radiotherapy (34%), 6 patients a chemotherapy (12%) and 7 patients a radiochemotherapy (14%).

The dominating regime of radiation was 60 gray in 30 fractions and a platinium-containing chemotherapy. In 45 patients details on recurrence and survival were reported. The median survival of these 45 patients was 6 months [range 0–40 months] with 39 patients (81%) dying within 12 months. One patient developed a local recurrence after 9 months and died after 14 month while our reported case developed a local and systemic recurrence after 37 months being still alive after 40 months. In seven cases a disease free survival was reported at 12, 15, 18, 20, 21, 24 and 26 months respectively [median 20 months; range 12–26]. None of these seven patients had a lymph node involvement and all received an adjuvant therapy (five times radiotherapy, one chemotherapy and one radiochemotherapy).

5. Discussion

Primary squamous cell cancer of the thyroid is a rare disease and mostly diagnosed at an advanced stage with poor prognosis [5]. Up to date there are only a few cases of PSCC of the thyroid described. The problem in analyzing PSCC is the differentiation of SCC primarily arising in the thyroid versus secondary SCC metastasis. Crucial for an accurate analysis of all PSCC cases is therefore an exclusion of all unproven primary cases. The right diagnosis of a PSCC of the thyroid is achieved through the combination of clinical, radiologic, endoscopic and immunohistologic findings. A computertomography of the neck and chest is necessary to exclude other sources of a squamous cell carcinoma which metastasized in the thyroid, e.g. from the larynx or lung [54,55]. By definition PSCC of the thyroid is entirely composed cells of squamous origin [1]. Immunohistochemistry can elucidate the typical cytokeratin pattern (CK 5/6 and CK 7) which is crucial to exclude an squamous cell carcinoma deriving or coexisting with a papillary carcinoma of the thyroid [51,56]. Further positivity of p53 and p63 as marker of poor differentiation in combination with Ki-67 can be helpful in making the right diagnosis [5]. Negativity for TTF-1 and thyroglobulin expression, both markers for follicular and papillary carcinomas, exclude the possibility of these common tumors [25].

The origin of PSCC of the thyroid is unclear and includes several unproven different hypothesis. Some suggest that squamous cells can originate from embryonic remnants containing squamous cells, such as the thyroglossal duct or the thymic epithelium [53]. Another theory assumes that squamous metaplasia of the follicular epithelium might develop due to the chronic inflammation in thyroiditis (e.g. Hashimoto thyroiditis) [27]. Our review shows 8 cases out of 45 with a lymphocytic infiltration of the thyroid next to squamous cell carcinoma, diagnosed as chronic thyreoidits.

Reviews by Syed et al. from 2011 and Cho et al. from 2014 reported 28 publication with a total of 84 cases of PSCC of the thyroid and 39 publication with 89 cases respectively [1]. Taking out the cases with lack of complete diagnostic work up as described above, only 49 patients from 35 publications remained available in our analysis (mainly due to a lacking immunohistochemistry). Disease free survival was only reported in seven patients with early tumor stage limited to the thyroid gland without lymph node involvement, complete surgical resection in combination with additional radiotherapy and/or chemotherapy. All other patients presented with advanced disease and succumbed irrespective of any treatment within the following 6-12 months. Lymphadenectomy and extended resections had no impact on patient survival. Many case reports suggest that PSCC of the thyroid is poorly responsive to either chemotherapy or radiotherapy concluding that any additional treatment to surgery can be omitted. However since

no data comparing the natural course of the disease versus palliative radiochemotherapy and surgery alone versus surgery and additional radiochemotherapy are lacking this conclusion should be considered cautiously. Furthermore all described cases with disease free survival received an additional radiotherapy and/or chemotherapy. In contrast to the review by Syed et al. who concluded that surgery, radiation and chemotherapy in any reported combination have little or no impact in improving outcome or prolonging survival and recommended palliative trachetomy our results show that a small number of patients with disease limited to the thyroid gland benefit from complete surgical resection in terms of a hemithyroidectomy or total thyroidectomy.

Squamous cell carcinomas, e.g. of the esophagus or the pharynx as well as larynx, are usually treated by radiotherapy [57]. Though, some reports declared squamous cell carcinoma of the thyroid to be radioresistant [3,34]. Our data show, that disease free survival greater 12 months was only achieved in seven patients with an early tumor stage without lymph node involvement, complete surgical resection in combination with additional radiotherapy and/or chemotherapy. However as presented in our case with a recurrence after 37 months real long term survival has not been reported in this pathology making cure within this disease doubtful.

Finally because of the highly aggressive course of PSCC of the thyroid we recommend that staging and treatment should be analog to that of anaplastic thyroid cancer. Surgical resection should be limited to cases with possible complete surgical resection in combination with adjuvant radio- and/or chemotherapy omitting resectional surgery in cases with airtract infiltration, metastatic cervical lymph nodes and distant metastasis. Cure is very unlikely in PSCC of the thyroid, as disease free long-term survival has not been reported in the literature yet.

Conflicting interests

Nothing to declare.

Funding

Nothing to declare.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

S.M. & F.S. contributed by designing, facilitating and planning the manuscript, collecting data, performing the interpretation, writing and revising the manuscript, and final approval of the submitted manuscript. M.Se., C.F., A.Ko & A.K. contributed by interpretation, revising and final approval of the submitted manuscript.

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Guarantor

Dr. Sven Müller accepts full responsibility for the work, had access to the data, and controlled the decision to publish.

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