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RESEARCH

Salvage surgery for cervical radioiodine refractory ^{18}F-FDG-PET positive recurrence of papillary thyroid cancer

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Abstract

Purpose: Five percent of patients with differentiated thyroid cancer are diagnosed with radioiodine refractory relapse in the course of the disease. For isolated or oligometastatic cervical recurrence, resection or another local treatment is recommended. In this study, the impact of surgical treatment of cervical radioiodine refractory ^{18}F-FDG-PET positive relapse of papillary thyroid cancer (PTC) was evaluated.
Methods: Patients receiving radioiodine therapy between 2005 and 2015 at the University Hospital of Cologne, Germany, for PTC were screened. The subgroup of patients undergoing surgery during the course of disease after recommendation by a multidisciplinary endocrine team for cervical radioiodine refractory ^{18}F-FDG-PET positive recurrence was identified. Demographics, clinic-pathologic characteristics, oncologic treatment, and outcome were analyzed.
Results: Thirty (3%) of 969 patients with PTC treated with radioiodine therapy at our institution underwent surgery for radioiodine refractory ^{18}F-FDG-PET positive cervical recurrence during the course of the disease. In eight (26.6%) patients, more than one operation was performed. Sixteen (53%) patients received external beam radiation therapy (EBRT) after surgery. Follow-up was on average, 79.2 ± 61.6 months after the last surgical treatment. Biochemical and radiological cure was seen in 12 (40%) patients. Remission was significantly more frequent in younger patients ($P = 0.0001$) with lymph node rather than soft tissue tumor recurrence ($P = 0.004$).
Conclusions: Surgical treatment of radioiodine refractory ^{18}F-FDG-PET positive cervical recurrence led to biochemical and radiological cure in about 40% of patients in this study. Further data are needed concerning risk stratification of potential subgroups benefitting of surgical approach and the possible role of EBRT after repetitive surgery.

Key Words

- radioiodine refractory disease
- salvage surgery
- external beam radiotherapy

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Introduction

Differentiated thyroid cancer (DTC) is often diagnosed postoperatively after resection of sonographic and/or cytological suspicious thyroid nodules. Since its prognosis is excellent in most cases, the main goals of surgery are, alongside with complete tumor resection, low morbidity, and satisfying cosmetic results (1). The use of prophylactic resection of clinically not involved central lymph nodes for papillary thyroid cancer (PTC), for example, is very controversial (2, 3, 4); it bears the risk of postoperative hypocalcemia, and radioiodine treatment (RAI) is known to treat micrometastatic disease (5).

The excellent response of DTC to RAI, besides its indolent behavior, is the main reason for its excellent prognosis. Even recurrence, which has been reported in 6.9–18% of patients within the first 5 years after initial treatment (6), can be healed by RAI re-challenge. However, in 33–55% of patients diagnosed with recurrence (7) and in approximately 5% of all DTC patients (8), all or some metastatic lesions become refractory to radioiodine treatment in the course of disease (RAI-R disease), impairing the, otherwise, excellent oncologic outcome (9).

The loss of the ability to uptake and concentrate radioiodine is not a histopathological but a clinical entity (8). Dedifferentiated nuclei and growth pattern, a high mitotic activity, and necrosis are unspecific signs that can be observed in RAI-R DTC metastases, but no specific pathological criteria are defined by the current WHO classification (8). Diagnosis is clinical and it is generally based on the combination of the lack of uptake in the radioiodine diagnostic whole-body scintigraphy scan (DWBS) and a pathologic uptake in ^{18}F-FDG-PET-CT, as a radiologic indicator of poor RAI effect of a lesion, as shown by a number of studies and recently by Kang *et al.* (7). ^{18}F-FDG-PET-CT uptake of DTC lesions, in general, has been found to be associated with a worse prognosis and decreased survival (10).

Besides some patients develop diffused metastatic disease, some other patients present isolated or oligometastatic cervical relapse in the form of either structural loco-regional soft tissue recurrence in the paratracheal space or lymph node metastases, involving the central and/or the lateral compartment. The Guidelines for the 'Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer' of the European Thyroid Association (ETA) recommend surgery or another local treatment for progressive single lesions or multiple lesions in a single organ (8). The decision concerning surgery, though, should weigh up the possible complications of repetitive surgery and the indolent nature of DTC as recommended by the American Thyroid Association (ATA) (11). Another important element in this decision-making process is the 'availability of surgical expertise specifically in the performance of revision thyroid cancer nodal surgery, which is a discrete surgical skill set', according to the ATA guidelines (11). In fact, there is currently no adjuvant systemic treatment that can eliminate residual disease and R0 resection is pivotal.

For inoperable cases or frequent structural recurrence after repetitive surgery, external beam radiation (EBRT) is a contemplated option in the ETA and ATA Guidelines (8, 11). It has been found to be associated with improved local disease control and a longer progression-free survival time in few studies (12, 13). However, evidence is still poor, and its side effects need to be considered, including the increased difficulty for potential repetitive surgery in the setting of irradiated tissue. Redifferentiation strategies are promising options currently tested in trials but are not established in the routine setting so far (14, 15).

While there is a risk of surgical overtreatment of most PTCs, given the excellent response to adjuvant RAI, it appears reasonable that patients at risk of developing radioiodine refractory relapse might benefit from aggressive primary resection with extended lymphadenectomy. For this reason, it might be of central importance to identify those patients at primary diagnosis. According to the Guidelines of the American Thyroid Association (ATA), the risk of recurrence is based on the TNM classification at baseline and on the response in 6–24 months after radioactive iodine ablation (11). However, this information is only available postoperatively. The BRAF mutation status, playing an increasing role in the risk stratification (11, 16), is sometimes available preoperatively and might play a role for guiding surgical treatment of primary tumors.

The aim of this study was to review our large patient cohort and to see which patients developed radioiodine refractory isolated or oligometastatic cervical PTC recurrence and underwent surgery as 'salvage surgery' in curative intention, among all PTC patients with intermediate or high-risk PTC, undergoing radioiodine treatment at our university endocrine center between 2005 and 2015. Their demographics and clinic-pathologic characteristics were analyzed; alongside with their oncologic treatment and their outcome, in order to evaluate the impact of surgery in those patients.

Methods

Patients

Patients receiving at least one radioiodine therapy between 2005 and 2015 at the University Hospital of Cologne, Germany, for papillary thyroid cancer were screened. Primary surgical treatment had been often performed in peripheral hospitals and these patients had been referred for radioiodine treatment and oncologic care with a thyroid carcinoma diagnosis to our center.

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The subgroup of patients undergoing another surgical procedure after recommendation by a multidisciplinary endocrine team (MDET) for cervical radioiodine refractory ^{18}F-FDG-PET positive recurrence in the course of the disease was identified. Demographics, clinic-pathologic characteristics, oncologic treatment, and outcome were analyzed. We chose to focus on papillary thyroid cancer in order to reduce heterogeneity and to focus on both lymph nodes and loco-regional recurrence being more prevalent in PTC than FTC.

Diagnosis of recurrence

Diagnosis of recurrence was based on physical examination, thyroglobulin increment, and imaging studies.

During follow-up, significant elevation of basal and stimulated serum TG compared to the nadir value and, in general, >1 ng/mL measured with an ultrasensitive assay led to the administration of 185–370 MBq of radioiodine (I-131) to obtain a diagnostic whole-body scintigraphy scan (DWBS). In case of low or absent radioiodine uptake, an ^{18}F-FDG-PET-CT was performed. If DWBS studies were positive, patients received a therapeutic activity of 3.7–7.4 GBq of radioiodine (I-131). If DWBS was negative, but ^{18}F-FDG-PET-CT confirmed structural recurrence (Fig. 1), salvage surgery was considered. If the imaging studies did not display recurrence, serum TG levels were monitored.

In the present study, 'early relapse' indicated recurrence within 12 months after thyroidectomy, whereas 'late relapse' after at least 5 years.

Surgery

Salvage surgery mostly consists of cervical re-exploration and resection, consisting in a resection of the local recurrence and/or in systematic lymphadenectomy. Indication to surgery was always initiated by the MDET. A limited number of pulmonary lesions were not an exclusion criterion for surgery in some patients, whereas surgery was generally not performed in patients displaying bone and/or other distant metastases unless a cervical metastasis was deemed close to invade important anatomic structure and cause problems for the patient. Those patients receiving palliative surgical resection, however, were excluded from this study, concentrating on surgery with curative intention.

Additional surgery in the first 3 months after thyroidectomy was supposed to be incomplete tumor clearance and was not considered 'salvage surgery'. After salvage surgery, all cases were discussed again regularly in the endocrine tumor board.

EBRT

External Beam Radiation Therapy (EBRT) was sometimes advised in case of histologically proven incomplete tumor clearance (R1/R2) with the aim to treat micro- and sometimes macroscopic residual disease. EBRT was also offered to patients requiring several cervical resections within a few months/years for loco-regional control, after thorough information concerning the poor current evidence and the possible side effects of treatment. Treatment decisions were individualized taking into account the patients' age, personal preferences, and potential side effects. External beam radiation therapy (EBRT) was performed either in palliative (50 Gy) or in curative intention (59.4–63 Gy) over 8 weeks.

Follow-up

Follow-up examinations took place yearly in the Department of Nuclear Medicine and included physical examinations, thyroglobulin level, DWBS, cervical

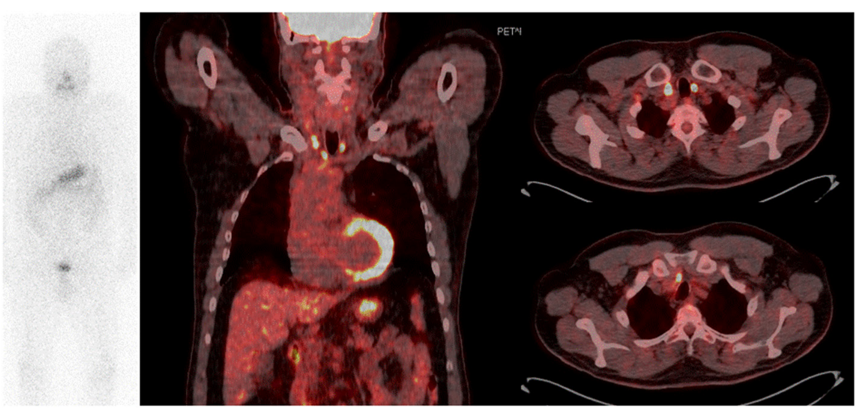

Figure 1
Negative I-131 diagnostic whole-body scintigraphy of a 54-year-old male with increasing thyroglobulin levels 80 months after thyroidectomy and ablative radioiodine treatment for a pT2 pN1(2/26) PTC. ^{18}F-FDG-PET showed three cervical tumors as the reason for the increasing TG. The patient underwent surgical removal consisting of a bilateral radical modified lymphadenectomy delivering eight metastases in 21 lymph nodes. EBRT was performed in an adjuvant setting. Nine years and 1 month after salvage surgery and EBRT, the patient was still free of disease (TG 0.1 ng/mL).

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ultrasound and/or MRI, and ^{18}FDG-PET-CT, if necessary. Mean follow-up was 79.2 ± 61.6 months after the last salvage surgery. Follow-up examinations until March 2, 2021 were included in this study. Response was evaluated according to the RECIST criteria.

Data collection and analysis

Electronic and paper data of the University Hospital of Cologne were retrospectively collected and analyzed. The study was approved by the ethical committee of the University Hospital Cologne.

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0.

Results

Patient characteristics

A total of 969 patients with intermediate or high-risk papillary thyroid cancer were treated with at least one radioiodine therapy after thyroidectomy in our department of nuclear medicine. One hundred fifty-four patients (16%) were treated by more than one RAI treatment, because of persisting elevated TG, as a sign of incomplete biochemical response or positive lesions in DWBS.

Thirty (3%) patients were diagnosed with structural cervical radioiodine negative, ^{18}F-FDG-PET positive recurrence in the course of the disease and underwent surgery. Table 1 summarizes their baseline characteristics including type of initial surgery, number, and doses of RAI courses, and type of surgical resection of RAI-R disease. The specific variants of papillary thyroid cancer were not regularly documented in the available records; therefore, they are not included. Molecular pathology, including *BRAF* mutation analysis, was not routinely performed between 2005 and 2015 at our institution.

Before the diagnosis of radioiodine-refractory ^{18}F-FDG-PET positive relapse, patients had received on average 2.1 ± 1.0 radioiodine treatments (range 1–5).

Patients undergoing surgery

This group of 30 patients comprised 7 male and 23 female patients (76.6%). Their mean age was 44.6 ± 17 (range 20–79 years). Three (10%) patients had T1, 5 (17%) T2, 13 (43%) T3, and 7 (23%) T4 status at the time of the first diagnosis. In two (6%) cases, the original T status was not available as the surgery had been performed several years before abroad. Twenty-four (86%) of the 28 patients with a complete TNM classification underwent either simultaneous cervical lymphadenectomy at the time of thyroidectomy or within the first three following months after thyroidectomy. In six (25%) cases, lymphadenectomy also included the lateral in addition to the central compartment. Lymphadenectomy yielded on average 25.7 ± 16.3 lymph nodes. Eighteen (75%) patients had positive lymph nodes at diagnosis.

Lung metastases (M1) were present in four (14.8%) patients at the time of first postoperative DWBS.

The mean interval from the date of thyroidectomy to the date of the first diagnosis of radioiodine-refractory ^{18}F-FDG-PET positive relapse was 56.4 ± 68.5 months. Early relapse in terms of relapse within 12 months after thyroidectomy occurred in seven (23%) patients. Late relapse in terms of relapse after 60 months occurred in eight (27%) patients.

Surgery

Eight (26.6%) patients underwent more than one cervical procedure, five (16.7%) patients received resection of pulmonary metastases additionally to cervical surgery. Twenty-two (44.9%) of 49 surgical procedures consisted in resection of local soft tissue metastases or isolated PET-positive lymph nodes instead of radical anatomic resections. Twenty-one (42.8%) of 49 the procedures performed were radical compartmental lymph node dissections, delivering 18 ± 15 lymph nodes on average. There were six resections of pulmonary metastases in five patients.

Thyroglobulin levels did not drop within normal ranges in seven (17%) patients after salvage surgery. No patient experiencing loco-regional radioiodine refractory PET-positive recurrence had TG antibodies at the time of their last follow-up, irrespective of disease group (cure, progress, or stable). Four patients had experienced elevated TG antibodies during the course of the disease.

EBRT

In 16 (53.3%) cases, EBRT was performed according to the recommendation of the MDET. In 14 (87.5%) cases, it was with curative intention, with the aim of reducing the risk of further recurrence in patients experiencing several relapses or R1 resection of metastases. In two cases (12.5%), EBRT was recommended in the course of the disease with palliative intention, because complete surgical removal was deemed not possible. The average age of patients

Table 1 Summarizes their baseline characteristics including the type of initial surgery, number of RAI courses, cumulative RAI activity, and type of surgical resection of RAI-R disease. The specific variants of papillary thyroid cancer were not regularly documented in the available records; for this reason, they are not included. In one case (Pt. 13) of a woman receiving radioiodine several years before in another hospital, the cumulative RAI activity of four previous RAI therapies was not available. In our Department for Nuclear Medicine, 7.4 GBq were administered as a fifth therapy 20 years after the previous four.

	Type of initial surgery	No. of RAI courses	Cumulative RAI activity (GBq)	Type of surgical resection of RAI-R disease
Pt 1	• TT and bCLND	1	3.7	• 5× resection of isolated LNs over 15 years.
Pt 2	• TT and bCLND	4	17.5	• Resection of one isolated LN
Pt 3	• TT and bCLND and iLLND	2	8.5	• 2× iLLND
Pt 4	• HT; • HT and bCLND	3	14.8	• Resection of one paratracheal ST metastasis
Pt 5	• HT; • HT	2	7.4	• Resection of one jugular ST metastasis
Pt 6	• HT; • HT and bCLND	4	16.5	• Resection of one paratracheal ST metastasis + iLLND
Pt 7	• HT; • HT	2	11.1	• Resection of one paratracheal ST metastasis + isolated lateral LN metastases; • 2× resection of pulmonary metastases
Pt 8	• TT and bCLND	3	14.8	• 2× iLLND
Pt 9	• TT and bCLND	1	5.5	• Resection of one paratracheal ST metastasis; • Resection of multiple pulmonary metastases
Pt 10	• TT and bCLND; • iLLND	2	12.9	• Resection of one ST metastasis dorsolateral of the trachea
Pt 11	• TT and bCLND	3	16	• iLLND; • cLLND
Pt 12	• TT and bCLND	3	18.5	• iLLND
Pt 13	• TT	5	n.d.	• iLLND; • Resection of pulmonary metastases
Pt 14	• TT and bCLND and bLLND	1	3.7	• Resection of one paratracheal ST metastasis + iLLND
Pt 15	• TT and bCLND	3	20.3	• iLLND
Pt 16	• TT and bCLND; bLLND	2	8.7	• iCLND
Pt 17	• nTT and bCLND	2	11	• 2× resection of paratracheal ST metastasis
Pt 18	• HT; • HT and bCLND	1	3.7	• Resection of paratracheal ST metastasis
Pt 19	• TT and bCLND	1	3.7	• Resection of isolated LNs; • iLLND
Pt 20	• TT and bCLND	2	8.9	• Resection of one paratracheal ST metastasis + iLLND
Pt 21	• TT and bCLND	1	3.7	• iLLND
Pt 22	• TT and bCLND	2	8.9	• 3× resection of paratracheal ST metastases
Pt 23	• nTT and bCLND	2	10.9	• iCLND; • Resection of one pulmonary metastasis
Pt 24	• TT and iCLND	1	5.5	• Resection of isolated paratracheal LNs
Pt 25	• HT; • HT and bCLND	2	11.1	• iLLND
Pt 26	• HT; • HT and bCLND	1	5.5	• iLLND
Pt 27	• TT and bCLND	4	25.9	• iLLND
Pt 28	• HT; • HT and bCLND	2	11.1	• iLLND
Pt 29	• HT; • HT and bCLND	1	5.4	• 3× resection of paratracheal ST metastases; • Resection of one pulmonary metastasis
Pt 30	• TT and bCLND	2	11.1	• iLLND

bCLND, bilateral CLND; bLLND, bilateral LLND; cCLND, contralateral CLND; cLLND, contralateral LLND; CLND, central lymph node dissection; HT, hemithyroidectomy; iCLND, ipsilateral CLND; iLLND, ipsilateral LLND; LLND, lateral lymph node dissection; LN, lymph node; n.d., not documented; nTT, near total thyroidectomy; Pt, patient; RAI, radioiodine ablation; ST, soft tissue; TT, total thyroidectomy.

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undergoing EBRT was 42.9 ± 18.7 years (range 19–75) and did not differ from that of patients without EBRT ($P=0.53$). The male: female ratio was 4:16 and 3:14, respectively ($P=0.39$).

In the group undergoing surgery and EBRT, seven (44%) patients are currently free of disease, two (12.5%) have stable disease, three (18.7%) show tumor progression, and four (25%) patients have died with diffuse pulmonary and bone metastases.

In the group undergoing surgery without EBRT, five (36%) patients are free of disease ($P=0.32$), six (42.8%) show stable disease, and three (21%) display progressive disease (Table 2).

Overall clinical course

Ten patients experiencing disease progression or death were on average 62.2 ± 14.7 (range 35–79) years old at the time of diagnosis of radioiodine-refractory ^{18}F-FDG-PET positive disease. Progression was only seen in patients with initial pT3 and 4 status. In these patients, recurrence manifested on average 48.6 ± 50.1 months after thyroidectomy. Surgery yielded on average 14 ± 12 lymph nodes and in six (60%) cases, loco-regional relapse. Seven (70%) patients underwent EBRT. Four (40%) patients had or developed pulmonary metastases in the course of the disease.

Twelve patients who are currently free of biochemical and/or radiological disease were significantly younger: on average 37.4 ± 10.3 years old (20–53 years, $P < 0.001$). Three (25%) patients had initial pT1, three (25%) pT2, four (33.3%) pT3, and two (16.7%) patients pT4 initial status. The time frame between thyroidectomy and relapse was similar between patients with progress and patients experiencing cure ($P=0.89$). Lymphadenectomy yielded on average 23 ± 25 lymph nodes ($P=0.28$). Loco-regional relapse was significantly less frequent (25% vs 60%, $P=0.048$). Seven (58.3%) patients underwent EBRT. In one case, pulmonary metastases were documented in external records of a young female patient before radioiodine treatment and disappeared in the course of treatment before cervical surgery of radioiodine refractory disease. In another case, a 0.7 cm metastasis was removed per VATS, leading to a normalized Tg level.

Incomplete biochemical response despite lack of radiologic disease was observed in six (20%) and stable radiologic disease in two (6.7%) of patients. Thus, disease control in terms of complete and incomplete cure and stable disease was seen in 20 (66.6%) patients undergoing surgery. These patients were significantly younger than patients experiencing progress ($P < 0.001$). Table 2 summarizes the characteristics of patients experiencing disease progression, complete (biochemical and radiological), and incomplete cure.

Table 2 In the upper part of the table, the outcome (progression, complete (biochemical and radiological), or incomplete cure/stable disease) of patients undergoing salvage surgery with or without EBRT for cervical radioiodine refractory relapse is depicted. Although the rate of progression and complete cure did not differ significantly, there were significantly more cases of incomplete cure/stable disease in patients, who did not undergo EBRT. In the lower part of the table, the characteristics of patients experiencing progression (column 1), complete (biochemical and radiological) cure (column 2), or incomplete (radiological but not biochemical) cure, or stable disease (column 3) are listed. Patients experiencing cure were significantly younger and had more frequent lymph node rather than local relapse in the fat surrounding the thyroid gland.

	Progress and/or death (P)	**Biochemical and radiological cure** (C)	**Biochemical and/or radiological stable disease** (S.D.)	***P*-value for P vs C and for P vs S.D.**
n	10 (6+4)	12	8	
Surgery (*n* = 14)	3 (21%)	5 (35.7%)	6 (42.8%)	
Surgery and EBRT (*n* = 16)	3+4 (43.7%)	7 (43.7%)	2(12.5%)	
P-value	0.1	0.3	**0.03**	
Patients receiving additional EBRT (*n* =) (%)	7 (70)	7 (58.3)	2 (25)	0.29, **0.02**
Age at the time of relapse diagnosis (years)	62.2 (±14.7)	37.4 (±10.3)	40.7 (±12.8)	**<0.001, 0.002**
Time frame between thyroidectomy and RAI-R relapse diagnosis (months)	48.6 (±50.1)	51.6 (±52.3)	31.8 (±27.1)	0.89, 0.38
Number of lymph nodes yielded by repeated surgery (*n* =)	14.2 (±11.5)	23.2 (±25.1)	10.6 (±9.9)	0.28, 0.48
Patients with loco-regional relapse in fat or soft tissue (*n* =) (%)	6 (60)	3 (25)	3 (37.5)	**0.048**, 0.17
Patients with pulmonary metastases (*n* =) (%)	4 (40)	2 (16.7)	2 (25)	0.11, 0.25

Bold indicates statistical significance, $P < 0.05$.

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Discussion

The 2019 ETA Guidelines state that 'whenever possible a local treatment, including surgery, should be preferred, and systemic therapy should be postponed until evidence of a multimetastatic progressive disease' (8). Recently Otsuki *et al.* described the outcome of 25 patients who underwent salvage surgery for structural local recurrence of PTC. They recommend judicious indications to surgery, due to the high risk of complications and sometimes reduced quality of life of patients after repetitive neck surgery (17). In addition, only 6 (24%) of the 25 patients included in their study were alive without disease and 4 (16%) had died, whereas the others had distant metastases. Thus, it is unclear if the benefits of salvage surgery exceed the complications, moreover because there is no standard adjuvant treatment afterwards.

In the present study, PTC relapse after surgery and radioiodine treatment occurred in 16% of patients and was managed with radioiodine re-challenge. This rate is consistent with the results reported by Shokoohi *et al.* for a Canadian population (18). Surgery for radioiodine refractory ^{18}F-FDG-PET positive relapse in terms of lymph node and/or loco-regional relapse was indicated in 3% of cases, also consistent with most literature (18). In some cases, a radioiodine refractory behavior was recognized directly after the first radioiodine treatment, in some cases, it developed during the course of the disease. Thus, patients receiving the diagnosis of radioiodine refractory ^{18}F-FDG-PET positive relapse had on average two radioiodine treatments before, in this study. It is still unclear, whether these tumors are refractory to radioiodine treatment from the beginning or if they developed a radioiodine refractory behavior during the course of the disease. On average, the diagnosis was made 56 months after thyroidectomy in this study, thus suggesting a slow development of radioiodine refractory disease.

Surgery consisted of a radically modified compartmental lymph node dissection in many cases. In some other patients however, single loco-regional recurrent tumors located in the paratracheal soft tissue or isolated lymph nodes, were surgically removed by 'berry picking' technique. Although 'berry picking' has been shown to be associated with an increased rate of recurrence (19), it was frequently performed in the time before the ATA and ETA guidelines. Although surgical accuracy during lymphadenectomy might reasonably influence the clinical outcome of surgery in a disease lacking a systemic treatment, the number of lymph nodes retrieved was not significantly different in patients experiencing cure in this study.

There is currently no systemic adjuvant treatment after surgery for recurrent differentiated thyroid cancer. Eight patients (26.7%) required more than one cervical operation and in half of all cases, the MDET recommended external beam radiation therapy for adjuvant treatment after repeated surgery or after R1 removal of metastases, in order to reduce the risk of recurrence. The ETA Guidelines (8) state that 'although RAI-R thyroid carcinomas are not very sensitive to radiation, external beam radiotherapy (EBRT) may be indicated in some specific cases' with the aim of stopping the growth or at least to reduce the rate of growth and prevent local symptoms. Thus 'recurrent lymph node metastases after repetitive surgery' are suggested as a possible indication and the studies of Hamilton *et al.* (12) and Chen *et al.* (13) are quoted, suggesting local disease control and a longer progression-free survival time.

The percentage of patients experiencing biochemical and radiological cure after surgery alone vs surgery followed by EBRT was not significantly different in this study (36% vs 44%, $P=0.32$). Our findings are not surprising since EBRT was generally recommended in cases of repeated recurrence, R1 resection, and when more advanced disease or risk situations were diagnosed, in the lack of an adjuvant medical treatment. The usefulness of EBRT in recurrent disease has been suggested by several authors (20, 21, 22), but solid prospective data are still lacking. No definitive recommendation can be made based on the results presented here.

Another observation in our study was the fact that patients who experienced biochemical and radiological cure were significantly younger, consistently with the recent increase of the age cut-off for risk stratification in PTC from 45 to 55 years in the TNM-8 (23): patients experiencing progression were older than 55 in this study. Recent data also confirm increased overall survival in patients with radioiodine refractory disease younger than 45 (24). A further result was that patients, who could not be cured by surgery, more frequently displayed loco-regional recurrence instead of lymph nodal recurrence. This confirms the generally assumed worse prognosis for patients with tumor relapse in fat or soft tissue (25). In fact, soft tissue metastases are often the 'tip of the iceberg'.

Finally, thyroglobulin antibodies, which have been recently suggested for monitoring the course of the disease or as a marker for the outcome, were not elevated or normalized in all patients in this study (26, 27), even in

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the subgroup experiencing disease progress. This should be taken into account, when interpreting the present data. It is unclear if patients with thyroglobulin antibodies might experience more aggressive disease.

Although this study has the limitations of a retrospective analysis and includes only a small collective of patients ($n = 30$), it describes the routine management of radioiodine refractory, ^{18}F-FDG-PET positive relapse at our university institution and its outcome, with a good rate of cure of 40%. Pulmonary metastases remain an important additional issue, which was not regarded sufficiently in this study. Finally, the lack of molecular profile of radioiodine refractory relapse and of precise specification of the PTC variants included should be regarded as a further limitation of the data presented. Further prospective data are still required to formulate evidence-based recommendations especially for patients, who are not cured by surgery. There is not much evidence on EBRT, and its use is very controversial due to the possible severe side effects, reducing the quality of life of patients and the indolent nature of papillary thyroid cancer, even in its radioiodine refractory variant.

Finally, preoperative strategies for the identification of patients at risk of developing radioiodine-refractory recurrence might guide the plan of primary surgical treatment, for example, concerning prophylactic central lymph node dissection in patients without preoperative evidence of lymph node involvement. A preoperative ^{18}F-FDG-PET scan (7) or molecular diagnostic on nodule cytology might, for example, deliver some additional information required to identify this small collective of patients with more aggressive tumors, requiring more aggressive treatment. Zelinskaya (28) described immunohistochemical determination of Tg expression in radioiodine refractory metastases (Tg-positive cells < 56%) as a possible diagnostic tool, for example. If this expression is already increased in the primary tumors with low radioiodine sensitivity or in primary tumors, which will develop radioiodine refractory behavior is still unclear and should be investigated in future studies.

Conclusions

Forty percent of patients undergoing surgery for ^{18}F-FDG-PET positive local recurrence currently experienced biochemical and radiological cure in this study. Evidence on the role of EBRT in RAI-R PTC is still limited and its side effects can be severe. It might be considered for patients with highly aggressive, frequently recurring PTCs because repeated surgical treatment could also bear major complications and reduce the quality of life.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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