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Lebensqualität bei Patienten mit Schilddrüsenkrebs – Der Einfluss von postoperativem Hypoparathyreoidismus

Quality of life in thyroid cancer patients – The impact of postsurgical hypoparathyroidism

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List of abbreviations

AL: appetite loss

ATA: American Thyroid Association

ATC: anaplastic thyroid cancer

BAETS: British Association of Endocrine & Thyroid Surgeons

CF: cognitive functioning

CO: constipation

DI: diarrhea

DTC: differentiated thyroid cancer

DY: dyspnea

EF: emotional functioning

EORTC: European Organisation for Research and Treatment of Cancer

EORTC QLQ-C30: The European Organisation for Research and Treatment of Cancer quality of life group core questionnaire

EORTC QLQ-F17: functioning scales of the EORTC QLQ-C30

EORTC QLQ-THY34: validated thyroid cancer module of the EORTC quality of life group

ePROs: electronic patient reported outcomes

FA: Fatigue

FACT-G: Functional Assessment of Cancer Therapy – General

FI: financial difficulties

HPES-Impact: Hypoparathyroidism Patient Experience Scale-Impact

HPES-Symptom: Hypoparathyroidism Patient Experience Scale-Symptom

HPQ-28: Hypoparathyroid Patient Questionnaire

hypoPT: hypoparathyroidism

MTC: medullary thyroid cancer

NHP: Nottingham Health Profile

NS-hypoPT: non-surgical hypoparathyroidism

NV: nausea and vomiting

PA: pain

PF: physical functioning

POSH: post-surgical hypoparathyroidism

PROs: patient reported outcomes

PTH: parathyroid hormone

RF: role functioning

SF: social functioning

SF-36: Medical Outcomes Survey 36-item short-form health survey

SL: insomnia

TC: thyroid cancer

THYCA-QoL: thyroid-cancer-specific quality of life questionnaire

QoL: quality of life

15D: health state descriptive system 15

1. Summaries

1.1 German abstract

Hintergrund

Mit einer alters-standardisierten Inzidenzrate von 6.6 pro 100000 Personen pro Jahr gehört Schilddrüsenkrebs zu den seltenen Krebserkrankungen. Schilddrüsenkrebs weist im Großteil der Fälle eine gute Prognose auf. Dennoch berichten Schilddrüsenkrebspatienten von Einschränkungen in der Lebensqualität. Hypoparathyreoidismus ist eine der häufigsten Komplikationen einer operativen Therapie von Schilddrüsenkrebs. Hypoparathyreoidismus wird durch Hypokalzämie und niedriges Parathormon definiert. Die Prävalenz liegt bei 5.3 - 40 pro 100000 Personen in verschiedenen Ländern. Auch Patienten mit Hypoparathyreoidismus berichten Einschränkungen in der Lebensqualität im Vergleich zu gematchten Kontrollindividuen oder Normpopulationen. Deshalb stellt sich die Frage, ob die Einschränkungen in der Lebensqualität von Schilddrüsenkrebspatienten auch zum Teil durch die Einschränkungen von Hypoparathyreoidismus erklärbar sind. Dies führt zu folgenden Forschungsfragen:

1. Welche Auswirkungen hat ein chronischer Hypoparathyreoidismus auf die Lebensqualität von Schilddrüsenkrebspatienten?

2. Verstärken sich die Lebensqualitätseinschränkungen von Schilddrüsenkrebs und Hypoparathyreoidismus gegenseitig?

Methoden

Drei Studien werden heranzogen um die Forschungsfrage zu beantworten. In Studie 1 wurden 75 Schilddrüsenkrebspatienten (mindestens 1 Jahr noch operativer Behandlung) eingeschlossen. 36 Patienten gaben an, dass sie seit ihrer operativen Schilddrüsenkrebsbehandlung Kalzium- und/oder Vitamin D Präparate einnehmen. 89 Schilddrüsenkrebspatienten, von denen zusätzlich 17 eine Diagnose eines Hypoparathyreoidismus hatten, bildeten die Stichprobe in Studie 2. Für Studie 3 wurden 264 Patienten mit Hypoparathyreoidismus mittels einer Online-Umfrage befragt. Zur Messung der Lebensqualität benutzten alle drei Studien den Hauptfragenbogen der Lebensqualitätsgruppe der European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30). In Studie 1 wurde zusätzlich noch der schilddrüsenkrebsspezifische Fragebogen der Lebensqualitätsgruppe der European Organisation for Research and Treatment of Cancer (EORTC QLQ-THY34) verwendet, in Studie 2 wurden zusätzliche Symptome abgefragt und in Studie 3 der Hypoparathyroid Patient Questionnaire (HPQ-28 verwendet).

Ergebnisse

In Studie 1 zeigte sich, dass die fortgeführte Einnahme von Kalzium- und/oder Vitamin D Präparaten (im Vergleich zu keiner Einnahme) einen signifikanten Effekt auf die Odds, eine schlechtere Lebensqualität in den Domänen Rollenfunktion (OR 4.63; 95% KI [1.28–19.77]) und emotionale Funktion (OR 3.87; 95% KI [1.11–15.42]) als eine Normpopulation zu haben. Studie 2 zeigte, dass Patienten mit Hypoparathyreoidismus (im Vergleich zu Patienten ohne Hypoparathyreoidismus) niedrigere Chancen hatten, höhere Werte (bessere Lebensqualität) in den Domänen globaler Gesundheitsstatus (OR: 0.29; 95%KI [0.10;0.80]), physische Funktion (OR: 0.22; 95%KI [0.08;0.58]), Rollenfunktion (OR: 0.27; 95%KI [0.10;0.75]), emotionale Funktion (OR: 0.20; 95%KI [0.07;0.60]) und soziale Funktion (OR: 0.30; 95%KI [0.10;0.87]) zu haben. In den Symptom-Skalen hatten die Patienten niedrigere Chancen für Müdigkeit (OR: 2.81; 95%KI [1.06;7.62], Schmerzen (OR: 4.47; 95%KI [1.62;12.67]), Atemnot (OR: 3.16; 95%KI [1.05;9.83]) und Schlaflosigkeit (OR: 4.49; 95%KI [1.59;12.90]). In Studie 3 zeigte sich, dass Patienten mit Hypoparathyreoidismus, bei denen Schilddrüsenkrebs die Ursache für den Hypoparathyreoidismus war, niedrigere Chancen hatten (im Vergleich zu Patienten mit nicht-operativem Hypoparathyreoidismus), im Bereich physische Funktion (OR: 0.1; 95%KI [0;0.5]) Einschränkungen von klinischer Bedeutung zu berichten.

Diskussion

Die Studien haben gezeigt, dass Schilddrüsenkrebspatienten mit postoperativem permanenten Hypoparathyreoidismus eine schlechtere Lebensqualität im Vergleich zu Schilddrüsenkrebspatienten ohne Hypoparathyreoidismus berichten. Mögliche Gründe können die Symptombelastung durch den Hypoparathyreoidismus, der Mangel an Parathormon oder die Komplikationen der langwierigen Hypoparathyreoidismusbehandlung sein.

In Leitlinien wird das Thema Hypoparathyreoidismus und Lebensqualität selten ausreichend adressiert. Häufig wird nur ein Bezug zur Behandlung von Schilddrüsenkrebs hergestellt. Auch findet in der klinischen Praxis kaum eine systematische Erhebung von Lebensqualitätsdaten bei Schilddrüsenkrebspatienten statt. Elektronische patientenberichtete Endpunkte könnten hier Abhilfe schaffen. Weiterhin berichten Schilddrüsenkrebspatienten (mit oder ohne Hypoparathyreoidismus) von unerfüllten Bedarfen in den Bereichen psychologische Unterstützung, Langezeitfolgen oder Selbsthilfe-Angebote.

1.2 English abstract

Background

Thyroid cancer is a rare cancer with an age-standardized incidence rate of 6.6 per 100000 individuals per year worldwide and generally has a good prognosis. Nevertheless, patients

with thyroid cancer report impairments in quality of life throughout the entire disease journey. One of the most prominent complications of surgical treatment for thyroid cancer is hypoparathyroidism. Hypoparathyroidism is defined by hypocalcaemia with inappropriately normal or low parathyroid hormone levels. The prevalence of hypoparathyroidism ranges between 5.3 to 40.0 per 100000 individuals among different countries. Patients with hypoparathyroidism report impairments in quality of life compared to matched controls and norm-populations. Therefore, the question arises whether the impairments in thyroid cancer patients' quality of life might also be attributable to hypoparathyroidism, resulting in the following research questions:

1. What is the impact of hypoparathyroidism on quality of life in thyroid cancer patients?

2. Do thyroid cancer and hypoparathyroidism compound each other, causing severe impairments for the patients?

Methods

Three studies are used for answering the stated research questions. Study 1 included 75 thyroid cancer patients who were at least one year post surgery, with 36 (48%) still reporting calcium and/or vitamin D intake. Study 2 consisted of 89 thyroid cancer patients with 17 reporting an additional diagnosis of hypoparathyroidism. Participants in study 3 were enrolled via an online survey that included in 264 hypoparathyroidism patients of whom 100 had surgical thyroid cancer treatment as the cause of their disease. Quality of life was assessed in all three studies using the European Organisation for Research and Treatment of Cancer quality of life group core questionnaire (EORTC QLQ-C30). Study 1 additionally used the thyroid cancer module of the European Organisation for Research and Treatment of Cancer quality of life group (EORTC QLQ-THY34), study 2 also used a hypoparathyroidism-specific symptoms list, and study 3 used the Hypoparathyroid Patient Questionnaire (HPQ-28).

Results

In study 1, current calcium or vitamin D intake (vs. no intake) had a significant effect on the odds of having a worse quality of life in role functioning (OR 4.63; 95% CI [1.28–19.77[) and emotional functioning (OR 3.87; 95% CI [1.11–15.42]) compared with the general population in role functioning (OR 4.63; 95% CI [1.28–19.77[) and emotional functioning (OR 3.87; 95% CI [1.11–15.42]). Study 2 indicated that patients in the hypoparathyroidism group had lower odds of reporting higher scores (better quality of life) compared to patients without hypoparathyroidism in global health (OR: 0.29; 95%CI [0.10;0.80]), physical functioning (OR: 0.22; 95%CI [0.08;0.58]), role functioning (OR: 0.27; 95%CI [0.10;0.75]); emotional functioning (OR: 0.20; 95%CI [0.07;0.60]), and social functioning (OR: 0.30;95%CI [0.10;0.87]). For symptom-scales, hypoparathyroid patients were more likely to have higher scores (more

symptom-related problems) in fatigue (OR: 2.81; 95%CI [1.06;7.62], pain (OR: 4.47; 95%CI [1.62;12.67]; dyspnoea (OR: 3.16; 95%CI [1.05;9.83]), and insomnia (OR: 4.49; 95%CI [1.59;12.90]). Study 3 showed that compared to non-surgical hypoparathyroid patients, hypoparathyroid patients with a history of thyroid cancer had lower odds of reporting clinically relevant impairments in quality of life for physical functioning (OR: 0.1; 95%CI [0;0.5]), while for all other scales no statistically significant associations were observed. The main predictor for impairments of clinical importance in quality of life was symptom burden assessed by the Hypoparathyroid Patient Questionnaire (HPQ-28).

Discussion

The studies show that patients with hypoparathyroidism as a surgical complication of thyroid cancer treatment reported worse quality of life compared to thyroid cancer patients without hypoparathyroidism. Potential reasons might be symptoms of hypocalcemia, parathormone deficiency itself, or the complications of long-term hypoparathyroidism treatment.

In guidelines, quality of life in relation to hypoparathyroidism is seldom addressed extensively and is mostly only related to the treatment of thyroid cancer. In clinical practice the assessment of quality of life in thyroid cancer is rarely performed, but electronic patient-reported outcomes might help to facilitate the implementation. Additionally, patients after thyroid cancer with and without hypoparathyroidism report unmet needs in various domains (e.g., psychological support, self-help).

2. Thyroid cancer

TC is a rare cancer with an age-standardized incidence rate of 6.6 per 100000 individuals per year worldwide. There is a large variation between the sexes, with age-standardized rates of 10.1 per 100000 per year for females and 3.1 per 100000 per year for males (1). For Germany the age-standardized incidence rates were 9.1 per 100000 inhabitants for females and 3.9 per 100000 in males in 2018. Numbers for 2022 are estimated to increase to 10.8 per 100 000 inhabitants in females and 4.5 per 100000 in males, making TC responsible for 1.8% and 0.7% of newly diagnosed cancers in Germany among females and males respectively. (2). The five-year prevalence in Germany is estimated to be 21100 cases among females and 8500 cases among males (2). This results roughly in a female to male ratio of 3:1, which is consistent across other countries and studies (3, 4). Compared to other cancers, TC often affects younger people, with almost half of the patients being below 50 years of age (5). Within the last decades the incidence of thyroid cancer has risen (6-9) but now seems to be stabilizing (10). There are ongoing debates if this rise is due to over diagnosis with better diagnostics tools (11-16), changes in risk factors (17), changes in classification or nomenclature (8, 18) , or if this rise reflects a true increase (19).

Survival rates and recommended treatment vary across the different types of TC. There are mainly three different types of TC.

a) Differentiated thyroid cancer (DTC)

DTC consists mostly of papillary thyroid cancer or follicular thyroid cancer and covers approximately 85% of all TC diagnoses (20). With 20-year survival of approximately 95%, DTC is considered to have a good prognosis (21, 22). The most common treatment(8, 18) is surgery followed by radioiodine treatment (20). Within the last years, discussions regarding papillary microcarcinomas have emerged. Papillary microcarcinomas are defined as papillary thyroid carcinomas with <10mm diameter with most tumors remaining small and clinically insignificant (23). Debates are focusing on whether treatment or active surveillance is the best option for these patients (24-27).

b) Medullary thyroid cancer (MTC)

MTC is responsible for approximately 5-10% of all TC cases (28, 29). Its survival rates are worse compared to DTC, with a 10-year survival of 75%-85% (30, 31). The main treatment for MTC is surgery. In advanced disease, treatment with tyrosine kinase inhibitor might be considered (32). In the 2022 WHO classification of thyroid tumors, a grading scheme for MTCs has been introduced as a recommendation for clinical risk assessment (33).

c) Anaplastic thyroid cancer (ATC)

Anaplastic thyroid carcinoma is the rarest subtype of TC, comprising approximately 1-2% of all TC cases (30, 34). ATC is an aggressive malignancy with high shares of lymph node metastases (56%) or distant metastases (38%) (35), resulting in poor survival of often less than six months (30).

As a result of the treatment or the disease itself, impairments in QoL frequently occur in TC patients (36-38). Three different types of patient-reported outcomes (PROs) have been used to measure QoL in TC patients:

a) Generic quality of life questionnaires/ PROs

Generic QoL questionnaires use broad and basic outcome dimensions which make the applicable for a big variety of medical conditions (39). The most often used generic quality of life questionnaire is the Medical Outcomes Survey 36-item short-form health survey (SF-36) developed by Ware et al. (40) in 1992 and its accompanying short forms SF-12 (41), and SF-8 (42). Other generic QoL tools are the health state descriptive system 15 (15D) (43) or the Nottingham Health Profile (NHP) (44). The advantages of generic QoL measurements are that they are applicable to all disease populations and healthy individuals they have been validated for. Additionally, using generic tools enables researchers to compare QoL between different diseases (45). Their biggest disadvantages are that they might miss disease-specific QoL impairments or symptoms and that they have high floor and ceiling effects (46, 47).

b) Cancer-specific quality of life questionnaire/ PROs

Cancer-specific QoL questionnaires address domains of QoL that are relevant for cancer patients. They address functional impairments and cover the most common symptoms of a cancer diagnosis or treatment (e.g. fatigue, pain). These tools are able to measure cancer patients' QoL in a more specific way than generic QoL questionnaires, but they still might miss symptoms or impairments in QoL related to a specific cancer type (45). The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group core questionnaire (QLQ-C30) (48) has been used in more than over 3000 studies worldwide and is available and validated in over 120 languages. It covers five functioning domains (physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), and social functioning (SF)), nine symptom domains (Fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnea (DY), insomnia (SL), appetite loss (AL), constipation (CO), diarrhea (DI), and financial difficulties (FI)) as well as one global quality of life scale (QL) (49). Another cancer-specific questionnaire that is often used is the Functional Assessment of Cancer Therapy - General (FACT-G). Using 27 questions it covers four domains (physical, social, emotional, and functional) of cancer patients' QoL and is available in 73 languages (50).

c) Thyroid cancer-specific quality of life questionnaire/ PROs

Since generic or cancer specific questionnaires do not cover all symptoms (e.g., problems swallowing) and QoL impairments (e.g., disease-related worries) of TC patients and do not include side effects specific to TC treatment (e.g., hypothyroidism, hypoparathyroidism), it is important to consider using a thyroid cancer-specific QoL tool. Various thyroid cancer-specific questionnaires exist (51-54) with the thyroid cancer-specific quality of life (THYCA-QoL) questionnaire by Husson et al. (55) being the most often used to date. The THYCA-QoL scales cover neuromuscular symptoms, voice, concentration, local symptomatic symptoms, throat and mouth, psychological and sensory complaints, scar problems, feeling chilly, tingling hands/feet, weight gain, headache, and reduced interest in sex (55). In 2023 Singer et al. (54) published the thyroid cancer module of the EORTC Quality of Life Group (EORTC QLQ-THY34). This questionnaire is used in addition to the EORTC QLQ-C30 in order to cover most cancer and thyroid cancer-specific issues in TC patients. The questionnaire comprises 17 scales (exhaustion, voice problems, hair problems, swallowing, treatment- and disease related worry, tingling or numbness, worry about important others, lacking social support, dry mouth, altered temperature tolerance, body image, shoulder functioning, joint pain, cramps, and impact on job or education) (54, 56, 57).

Roth et al. (58) conducted a systematic review in 2020 to investigate which PROs are used to assess QoL in TC patients. They only included studies that used the tool in English, and studies were excluded if they focused on only specific aspects of TC treatment or did not investigate the full spectrum of QoL in TC patients. Of the 927 publications found, 23 studies using validated QoL instruments were included in the systematic review. With the option of multiple questionnaires being used in one study, 10 (44%) studies used the EORTC QLQ-C30, 8 (35%) the SF-36, 5 (22%) the THYCA-QoL, 2 (9%) studies the City of Hope Thyroid Module (59), and 1 (4%) the University of Washington Quality of Life Questionnaire (60), the PROMIS-29 (61) or the THYCAT (51) respectively. The EORTC QLQ-THY34 was only published recently and was therefore not included in this systematic review.

Most of the studies evaluating QoL in TC patients used one of the described tools. The majority of studies reported impairments in QoL in some or all of the QoL domains (36-38), while only very few studies report QoL equivalent to a general population (62-64).

Impairments in QoL of TC patients can be found throughout the entire disease process; from diagnosis to long-term survivorship. Hedman et al (65) reported in their study that 75% of study participants had a fear of recurrence and 23% a negative view on life at diagnosis. These patients reported a lower QoL in five out of eight SF-36 domains compared to patients without fear of recurrence. After treatment for TC including surgery (66-68) or radioiodine treatment (69, 70), impairments in QoL have been reported due to potential side effects of the respective treatments. Studies have shown that patients after treatment receiving thyroid hormone

replacement have worse QoL compared to healthy controls or the general population (71-74). Patients in rehabilitation after TC report lower QoL compared to a general population after adjustment for age and sex (75). Even in TC survivors, impairments in QoL persist and specific symptoms (e.g. tingling, fear, exhaustion) remain (76-79), with a QoL equal or worse to the QoL of cancers with a worse prognosis (80).

3. Hypoparathyroidism

Hypoparathyroidism (hypoPT) is a rare endocrine disorder defined by hypocalcaemia with inappropriately normal or low parathyroid hormone levels (81-83). The main reason for hypoPT is removal of or damage to the parathyroid glands during thyroid surgery (84, 85). Approximately 75% of hypoPT cases are post-surgical (84). Risk factors for post-surgical hypoPT (POSH) are described in Section 3. The remaining 25% are due to autoimmune problems or to genetic origins, but the main cause of these non-surgical hypoPT (NS-hypoPT) remains unclear and therefore idiopathic (86, 87). The prevalence of hypoPT lies between 5.3 – 40.0 per 100 000 individuals in different countries (86, 88-93) with details presented in table 1. There are several reasons that may explain these huge variations. First, the number of thyroidectomies performed may vary between the different countries and therefore affect the number of POSH cases. In the future, a higher variation in these numbers might occur depending on the preferred treatment of papillary microcarcinomas (surgery vs. active surveillance) (24-27). Secondly, the year of diagnosis has a wide range, from 1981 in Israel (94) to 2020 in South Korea (95) resulting in differences in the occurrence of risk factors or changes in treatment. Thirdly, different data sources of varying quality and availability were used. Lastly, the assessment and definition of hypoPT varied between the studies. Some studies rely on ICD-codes written in discharge letters (93, 95) while other studies were able to check individual patient data (86, 91, 92). Different definitions of hypoPT is not only a problem related to studies evaluating the prevalence, but also for other endpoints, including studies on quality of life. Two systematic reviews have investigated the different definitions of hypoPT used in studies. In 2019, Harslof et al. (96) identified 89 studies that used 20 different definitions of hypoPT. Of these 89 studies, 16 (18%) did not report how hypoPT was defined. Mehanna et al. (97) performed a systematic literature review in 2009 to identify different definitions of hypoPT and applied the different definitions to a patient sample of 202 patients undergoing total or hemithyroidectomy. The ten different main definitions used in the studies led to an incidence of post-surgical hypoPT ranging from 0 to 46%. Another aspect which makes correct definitions of hypoPT difficult is the possibility that parathyroid glands may regain their original functioning after more than a year. While most studies and guidelines use a six-month timeframe to consider postsurgical hypoPT as permanent, Benmiloud et al. (98) und Villaroya-Marquina et al. (99) have shown that few patients who were diagnosed with permanent hypoPT after six months recovered from the disease one year after surgery. This

variation in definitions and time frames might also influence the results for the incidence of postsurgical hypoPT presented in Section 3.

Table 1 Details of studies measuring the prevalence of hypoPT

Country	Authors	Year	Prevalence per 100 000	Definition of hypoPT	Data source
Norway	Astor et al.	2016	Total: 9.4 POSH: 6.4 NS: 3.0	serum calcium below reference range with simultaneously low or inappropriately normal PTH	Electronic hospital registry
Israel	Zlotgora & Cohen	1981	NS: 7.0	NA	NA
Italy	Cipriani et al.	2017	Total: 5.3	Identification via ICD codes or combinations of ICD codes	Registry of the Italian health ministry
South Korea	Kim et al.	2020	NS: 1.1	ICD codes	National Health information database
Japan	Nakamura et al.	2000	NS: 7.2	Registered as hypoPT in hospital files	Reports from medical departments contacted via mail survey
USA	Clarke et al.	2016	Total: 37.0	Diagnosis of hypoPT in medical records	Longitudinal epidemiologic study
Italy	Cianferotti et al.	2018	Total: 27.0	Hospital discharge codes in combination with pharmaceutical codes	Electronic health records database of an Italian

					region (Tuscany)
Denmark	Underbjerg et al.	2013/2015	Total: 24.3 POSH: 22.0 NS: 2.3	POSH was defined as hypocalcaemia (plasma calcium below the lowest reference level) with inappropriately low PTH levels following neck surgery that necessitated treatment with calcium and/or vitamin D analog supplementation for more than 6 months	National Hospital patient registry
Scotland	Vadiveloo et al.	2018	Total: 40.0 POSH: 23.0 NS: 17.0	Patients had to fulfill 5 criteria including ICD codes, calcium intake and laboratory parameters	Population based dataset in Tayside, Scotland

POSH: post-surgical hypoPT
NS: non-surgical hypoPT

When hypoPT is diagnosed, the standard treatment consists of calcium and/or vitamin D supplementation, as hypoPT is the only endocrine disorder where the missing hormone cannot be replaced (82). Within the last years, synthetic parathyroid hormones (rhPTH (1-84) and rhPTH (1-34)) have shown promising results for the treatment of hypoPT (100-104). In 2017, the EMA approved NATPAR for the treatment of patients whose hypoPT could not be controlled by standard treatment. As of October 2024, Takeda, the producer of NATPAR, has announced an end to production due to unresolved supply issues (105). TransCon PTH, which has recently finished Phase 3 testing, is the only synthetic parathyroid hormone that has a chance of being approved in the next years (106-109). Without approval, patients will have to

continue the standard treatment which also comes with potential side effects und complications such as nephrocalcinosis or cataracts (110, 111). Patients receiving standard treatment report impairments in quality of life compared to matched controls or general populations. All five studies included in our systematic review (112) used generic quality of life questionnaires and therefore might suffer from the limitations resulting from these instruments (see Section 1). In recent years, two disease-specific questionnaires have been developed and validated: The Hypoparathyroid Patient Questionnaire (HPQ-28) (113) and the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom) (114, 115). The Hypoparathyroidism Patient Experience Scale-Impact (HPES-Impact) (116) is not yet validated. The HPQ-28 was validated in German hypoPT patients and contains eight scales (depression and anxiety, loss of vitality, pain and cramps, neurovegetative symptoms, gastrointestinal symptoms, numbness or tingling, memory problems, heart palpitations). General population data for the HPQ-28 is currently being collected and analysed and will be available in the near future. The HPES-Symptom was developed by a consultancy (The Brod Group) and a pharmaceutical company (Ascendis Pharma) and was validated in hypoPT patients in the US. Seventeen items result in two domains: physical (12 items) and cognitive (5 items). Both questionnaires contain items (e.g. tingling or numbness, cramps) that are also found in thyroid cancer-specific questionnaires such as the EORTC QLQ-THY34 (54) and the ThyCaQOL (55). Studies investigating the quality of life of hypoPT patients show that impairments compared to matched controls or norm-populations exist (86, 112, 117-119). For example, Astor et al. (86) showed that hypoPT patients had statistically significant lower scores across all eight domains of the SF-36 compared to a general norm population. Post-surgical hypoPT patients in this study had lower QoL scores than patients with Addison's disease (6 out of 8 domains) and adrenal hyperplasia (five out of eight domains) (120, 121). In order to exclude the potential effects of hypothyroidism Sikjaer et al. (119) performed a cross-sectional study with three groups of 22 patients each: (1) patients with chronic postsurgical hypoPT and well-substituted hypothyroidism, (2) patients with postsurgical well-substituted hypothyroidism without hypoPT, and (3) healthy controls without abnormalities in their thyroid or parathyroid function. The groups were matched for age, sex, and time of thyroid surgery. Compared to group 3, the hypoPT patients had statistically significant lower scores in all SF-36 domains except for the role emotional domain. The hypoPT patients also had statistically significantly lower scores in the physical functioning and role-physical domains compared to the patients in group 2. Whether this association between hypoPT and QoL also influences QoL in patients after treatment for TC is to be investigated.

4. Post-surgical hypoparathyroidism after thyroid cancer

Surgery for thyroid cancer is one of the main causes of postsurgical hypoPT. Large studies have reported shares from 20-40% for transient, and 5-12% for permanent hypoPT after

surgery for TC (122-126). In pediatric patients the shares range from 4.5-32% for transient, and 0-32% for permanent hypoPT (127-132). This heterogeneity in results may be explained by several factors. As described in Section 2 there is a huge variety in definitions of hypoPT, which contribute to different numbers of cases (96, 97). The timing of the assessment of hypoPT can have an impact on the shares. Recent studies have shown that it is possible for parathyroid glands to return to proper functioning after more than one year (98, 99). As various risk factors associated with post-surgical hypoPT haven been identified, their different distributions within the studies might also explain the differences found in the studies. The extent of surgery is one of the main risk factors for post-surgical hypoPT, with patients receiving total thyroidectomy having higher odds of developing permanent hypoPT compared to partial or hemi-thyroidectomy (126, 133-136). If neck dissection (137-141) or lymph node dissection (133, 140, 142, 143) are performed, the odds of developing permanent hypoPT are also increased. This association has led to recommendations in guidelines advocating against prophylactic neck dissection (144-146) (see Section 9.1.2). Another risk factor for the development of post-surgical hypoPT is the experience of the surgeon, with high volume surgeons reporting lower rates of hypoPT independent of the surgical volume of their centre (133, 138, 139, 147-149). Lorenz et al. (149) state that a surgeon can be considered a high volume surgeon if he or she performs at least 50 thyroidectomies per year. Results regarding autotransplantation of parathyroid glands in order to prevent hypoPT are inconsistent. While some studies found a higher impact on post-surgical hypoPT when autotransplantation of parathyroid glands was performed (123, 135, 150-152), these findings could not be confirmed by other studies (84, 153, 154). If parathyroid glands are found in the specimen, the risk of hypoPT is increased (133, 135, 155). As most risk factors are associated with surgery, it has been advocated that surgery for TC should only be performed by high volume surgeons with experience in parathyroid surgery in order to minimize the risk of post-surgical hypoPT (126, 149).

5. Quality of life in patients with thyroid cancer – the impact of hypoparathyroidism: current evidence from the literature

As seen in Sections 1 and 2, patients with TC and patients with hypoPT report impairments in QoL. Since post-surgical hypoPT is one of the major complications of TC treatment (see Section 3), the question arises whether impairments in QoL of TC patients might partially be explained by the negative effects from post-surgical hypoPT on QoL. A systematic literature search identified 12 studies investigating the QoL of TC patients that metioned the topic of hypoPT. Three studies only stated the incidence of hypoPT in their study populations without including hypoPT in their analyses (62, 156, 157). No influence of hypoPT on TC patients' QoL was observed in two studies (78, 158), leaving seven studies that included hypoPT in their analysis or reported an association between hypoPT and QoL. Vy et al. (159) performed a

cross-sectional study in 162 TC patients after surgery. They reported that hypoPT, vocal cord palsy or hypothyroidism significantly affected the patients without analyzing or quantifying this. In a study of 146 TC patients by Huang et al. (160), tetany and tingling around the mouth was present in patients with post-surgical hypoPT. Alyoussef et al. (161) also reported that tingling in the hand or the feet caused by hypocalcemia was one of the most common symptoms in their study of long-term (5-15 years) TC survivors. Bongers et al. (162) used calcitriol supplementation as an indicator for hypoPT and found an impact of the disease on the body image scale of the EORTC QLQ-THY34. Compared to TC patients without hypoPT, TC patients with hypoPT reported statistically significantly lower scores across all or various domains of the respective questionnaires used (76, 163, 164).

Seeing the impairments in QoL of TC patients potentially influenced by hypoPT, the question arises whether impairments in QoL among hypoPT patients might also be affected by TC and its treatment. In total 31 studies addressing the topic of QoL in hypoPT were identified in a systematic literature search in September 2023 by the author of this thesis. TC as an exclusion criterion was mentioned for two studies, and eight studies included TC in their analysis or at least in their discussion. Siggelkow et al. (165) found in their study of 398 hypoPT patients that mean SF-36 Physical Component and Mental Component scores of the patients were comparable or lower than the scores of cancer patients. In 2016 Sikjaer et al. (119) performed a study which compared the QoL of hypoPT patients to patients with hypothyroidism and healthy controls (see Section 2). Even though in the hypoPT group more patients had a diagnosis of TC five years before and the authors acknowledged that it might influence QoL, it was not included in the analysis. The remaining six studies (118, 166-170) included TC in their analysis of QoL but did not find any statistically significant association. None of the studies reported possible explanations for not finding any effect. Two studies (118, 166) included TC only in univariate analysis and might therefore be susceptible for confounding. With small sample sizes in the studies (168-170) lacking statistical power to find any association might be another possible explanation. In Büttner et al. (171) it is assumed that cancer patients may seek more support services that may help the patients to cope with their burden and therefore might help to maintain a good QoL. Nevertheless, the possibility also exists that this a true finding and TC is not associated with QoL in hypoPT patients.

6. Aim of the thesis and research question

Studies analyzing the QoL of TC patients have seldom included HypoPT in their analysis and vice versa the rare inclusion of TC in the analysis of hypoPT patients' QoL, this thesis addressed the following research questions:

1. What is the impact of hypoPT on QoL in TC patients?

2. Do TC and hypoPT compound each other, causing severe impairments for the patients?

As these research questions cannot be answered by single studies, I will present three studies that add information to the body of literature in order to answer these research questions.

7. Setting and methods of the three publications

All three publications (171-173) were published between 2020 and 2022. For all three publications, Matthias Büttner was the first and corresponding author. Ethical approval was obtained for the studies when required (Landesärztekammer Rheinland-Pfalz: #837.238.16 and # 837.470.14.9709).

7.1 Büttner et al. (2020) - Quality of life of patients more than 1 year after surgery for thyroid cancer

Study design: single centre (University Medical Centre Mainz) cross-sectional study

Study population: Patients with surgery for TC between 2010 and 2015 at the University Medical Center Mainz with parathyroid hormone or calcium levels below the reference values after surgery. Of 134 eligible patients, 75 (56%) participated in the study.

Definition/ diagnosis of hypoPT: Self-reported diagnosis of hypoPT by the patients. Additionally, patients stated if they were currently on calcium and/or vitamin D supplementation after surgery for TC.

HypoPT population: Four (5.3%) self-reported a diagnosis of permanent hypoPT and 36 (48.0%) reported calcium and/or vitamin D intake.

Assessment of QoL: Patients participated in a telephone interview where they completed the EORTC QLQ-C30, the EORTC QLQ-THY34, and a symptom list of typical hypoPT symptoms (e.g. tingling, trousseau sign), which was obtained from the literature and patient reports with a four-week time frame.

7.2 Büttner et al. (2020) - Quality of life in patients with hypoparathyroidism after treatment for thyroid cancer

Study design: multi-national cross-sectional study

Study population: Patients were enrolled for the Phase III study of the development of the EORTC QLQ-THY34 questionnaire. In total, 182 patients from 14 centers participated in the study. Inclusion criteria for this analysis were (i) clear information on parathyroid insufficiency and (ii) diagnosis of TC at least nine months past to ensure permanent hypoparathyroidism. These inclusion criteria resulted in 89 patients being eligible for the analysis.

Definition/ diagnosis of hypoPT: Diagnosis of hypoPT was confirmed and documented by the treating physician.

HypoPT population: Of the 89 TC patients fulfilling the inclusion criteria for the analysis 17 were additionally diagnosed with post-surgical hypoPT.

Assessment of QOL: Patients filled out the EORTC QLQ-C30 and the EORTC QLQ-THY34.

7.3 Büttner et al. (2022) - What are predictors of impaired quality of life in patients with hypoparathyroidism?

Study design: cross-sectional study with data obtained via an online survey

Study population: Patients with hypoPT were recruited through their treating physician or the newsletters or forums of self-help organizations. In total 264 hypoPT patients participated in the survey

Definition/ diagnosis of hypoPT: Patients with a self-reported diagnosis of hypoPT participated in the study

Thyroid cancer population: Of the 264 hypoPT patients, 100 (41.2%) stated that surgery for thyroid cancer was the cause of their hypoPT.

Assessment of QoL: The functioning scales of the EORTC QLQ-C30 (EORTC QLQ-F17) and the HPQ-28 were used to assess QoL and symptom burden.

8. Publications

The three following publications (including a German summary) are the basis for this thesis:

1. **Büttner M**, Hinz A, Singer S, Musholt TJ. Quality of life of patients more than 1 year after surgery for thyroid cancer. Hormones (Athens). 2020;19(2):233-43.

2. **Büttner M**, Locati LD, Pinto M, Araujo C, Tomaszewska IM, Kiyota N, et al. Quality of life in patients with hypoparathyroidism after treatment for thyroid cancer. J Clin Endocrinol Metab. 2020;105(12).

3. **Büttner M**, Krogh D, Siggelkow H, Singer S. What are predictors of impaired quality of life in patients with hypoparathyroidism? Clin Endocrinol (Oxf). 2022;97(3):268-75.

8.1 Büttner et al. (2020) - Quality of life of patients more than 1 year after surgery for thyroid cancer

Zusammenfassung

Einleitung: Es wird häufig angenommen, dass Patienten mit Schilddrüsenkrebs, aufgrund der guten Prognose, keine Einschränkungen ihrer Lebensqualität aufweisen. Der Einfluss von Folgen der Operation und die Notwendigkeit der lebenslangen Medikamenteneinnahme auf die Lebensqualität wurde bisher selten untersucht.

Methoden: Patienten, die zwischen 2010 und 2015 aufgrund einer Schilddrüsenkrebsdiagnose an der Universitätsmedizin Mainz operiert wurden und deren Parathormon- und Kalziumwerte postoperativ unter dem Referenzwert lagen, wurden als teilnahmefähig angesehen. Die Lebensqualität wurde mit dem EORTC QLQ-C30 und dem Schilddrüsenkrebs spezifischen Modul EORTC QLQ-THY34 erhoben. Multiple logistische Regression wurde durchgeführt um Bereiche zu identifizieren in denen die Patienten eine niedrigere Lebensqualität, im Vergleich zur Allgemeinbevölkerung, auswiesen.

Ergebnisse: Insgesamt 75 (56%) der 134 teilnahmefähigen Patienten nahmen an der Studie teil. Patienten, die seit der Operation Kalzium- und/oder Vitamin D Supplemente einnehmen, berichteten eine schlechtere Lebensqualität in den Bereichen globaler Gesundheitsstatus, physische Funktion, Rollenfunktion, emotionale Funktion und Schlaflosigkeit im Vergleich zu Patienten ohne Supplementation. Kalzium- und/oder Vitamin D Supplementation, höherer Bildungsgrad, Partnerschaft und Alter erhöhten die Odds eine schlechtere Lebensqualität im Vergleich zu einer alters- und geschlechtsadjustierten Allgemeinbevölkerung zu haben.

Fazit: Patienten, die mindestens ein Jahr nach ihrer Schilddrüsenkrebs-Operation noch Kalzium und/oder Vitamin D einnehmen, berichten Lebensqualitätseinschränkungen in verschiedenen Bereichen. Deshalb ist es wichtig, dass in der Nachsorge von Schilddrüsenkrebspatienten Kalzium und Vitamin D regelmäßig kontrolliert wird und dass Patienten mit diagnostiziertem Hypoparathyreoidismus besondere Aufmerksamkeit seitens des behandelnden Arztes erfahren.

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ORIGINAL ARTICLE

Quality of life of patients more than 1 year after surgery for thyroid cancer

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Abstract

Purpose Patients with thyroid cancer are often assumed to have no quality of life (QOL) impairments after treatment because of thyroid cancer's good prognosis. However, the QOL implications of surgical complications and the necessity to take lifelong medication are seldom assessed.

Methods Patients who had surgery due to thyroid cancer at the University Medical Center Mainz between 2010 and 2015 and who had calcium or parathyroid hormone levels below the reference values immediately following surgery were eligible for this study. QOL was assessed using the EORTC QLQ-C30 and the thyroid cancer module EORTC QLQ-THY34. Multiple logistic regression was used to determine factors associated with a worse QOL compared with a general population.

Results A total of 75 (56%) of 134 eligible patients participated in the study. Patients with persistent/prolonged calcium or vitamin D intake reported worse QOL in the domains of global health, physical functioning, role functioning, emotional functioning, and insomnia than patients without current intake. Current calcium and vitamin D intake, higher education, living with a partner, and age had an effect on the odds of having worse QOL than the age- and sex-adjusted general population.

Conclusion Prolonged calcium and/or vitamin D intake are negatively associated with certain domains of QOL in thyroid cancer patients who are at least 1 year post surgery. Assessment of calcium and vitamin D and diagnosis of hypoparathyroidism are therefore important for the follow-up of thyroid cancer survivors since it may affect their QOL.

Keywords Quality of life · Thyroid cancer · Calcium · Vitamin D

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Introduction

With an incidence rate of 6.3 per 100,000 per year and a mortality rate of 0.4 per 100,000 in Europe, thyroid cancer (TC) is considered to be a very treatable type of cancer [1]. Depending on the histology of TC, 10-year survival rates range from 95% for papillary or follicular types [2] and between 75% and 85% for medullary TC [2–4]. For anaplastic TC, median survival is less than 6 months [2]. Due to the general good prognosis of TC, it is often considered a "good" cancer, but this impression overlooks the associated morbidity [5]. Various studies have evaluated the quality of life (QOL) of TC patients and found impairments [6–8]. QOL impairments were also reported in long-term TC survivors up to 15 years post diagnosis [9–11]. Unfortunately, few of the studies assessing QOL in TC patients have reported data on postsurgical complications such as vocal cord palsy or hypoparathyroidism (HPT) resulting in symptomatic hypocalcemia [12, 13]. The British Association of Endocrine and Thyroid surgeons reported a rate of 23.5% (95% CI 22.7–24.5%) of

postoperative hypocalcemia, defined as low calcium on postoperative day 1 following total thyroidectomy [14]. A total of 60–70% of these hypocalcemia cases are only transient and resolve within 4–6 weeks after thyroid surgery [15]. Those individuals in whom hypocalcemia does not resolve within 6 months are considered to be permanent hypoparathyroid patients [16]. However, improvements are occasionally reported following more than 1 year. HPT is an endocrine disorder where replacement of the missing hormone is not the standard treatment. The current treatment consists of calcium supplementation and active forms of vitamin D [17]. However, calcium and vitamin D supplementation do not restore physiological calcium/phosphorus homeostasis, but rather lead to pronounced fluctuations in blood calcium levels. Despite lifelong intake, short-term complications such as brain fog, tingling in the fingers, arms, or legs, and other physical, cognitive, or emotional symptoms [18] as well as long-term complications such as kidney stones, soft tissue calcification, and renal failure are observed [19, 20]. Studies looking at an association between hypoparathyroidism and mortality show contradictory results [20, 21]. Patients with hypoparathyroidism report a worse QOL than patients from the general population or healthy controls [22].

The aim of this study was to evaluate QOL more than 1 year after surgery in patients who had low calcium and/or parathyroid hormone levels within 24 h following surgery and to identify factors that might influence their QOL. Additionally, the study aimed at identifying patients with and without calcium and vitamin D supplementation more than year after surgery and to assess their QOL compared with a general population.

Methods

Design and patient selection

The study was a single-center, cross-sectional study. Patients were eligible if they had surgery for thyroid cancer between 2010 and 2015 at the University Hospital Mainz, Germany, and if they met the following inclusion criteria: (i) histologically confirmed diagnosis of thyroid cancer, (ii) parathyroid hormone level below 20 ng/l and/or serum calcium levels below 2.1 mmol/l within 24 h after surgery for thyroid cancer, (iii) 18 years of age or older at the start of the study, and (iv) written informed consent. Patients were excluded if language skills or mental abilities to complete the questionnaires were lacking. The reason for selecting patients with low calcium or PTH levels was that we wanted to include a high proportion of patients with calcium and/or vitamin D intake after thyroid cancer treatment. Patients were approached by their treating physician by letter and received written information about the study. After having given their informed consent, patients were interviewed via telephone by a trained interviewer. Patients with interview data were considered to be participants, while patients who did not participate in the interview were considered to be non-participants. Additional medical information was obtained from the patients' health records. This study meets the ethical guidelines of the institution where the study was performed and was approved by the relevant ethical committee.

Assessments

For assessment of the QOL of the patients, the European Organization for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) and the newly developed EORTC QOL module for thyroid cancer (EORTC QLQ-THY34) were used. The EORTC QLQ-C30 is a tool that has been specifically developed to assess QOL in cancer patients and has been used in various studies. It consists of 30 items summarized into five functioning scales (physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF), global quality of life (QL)) and nine symptom scales (fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnea (DY), insomnia (SL), appetite loss (AL), constipation (CO), diarrhea (DI), and financial difficulties (FI)). All items are scored on a four-point Likert scale ("not at all," "a little," "quite a bit," and "very much"); only the QL scale–related items are scored on a seven-point Likert scale ranging from "very poor" to "excellent." The EORTC QLQ-THY34 is a newly developed module that accompanies the EORTC QLQ-C30 and specifically assesses the QOL issues of thyroid cancer patients that are not covered by the C30. The THY34 is currently in its final validation phase [23, 24] and consists of 34 items assessed via a four-point Likert scale summarized in the following scales: discomfort in the head and neck (DIN), fatigue (FA_THY), fear (FE), hair problems (HA), restlessness (RE), social support (SO), swallowing (SW), worry about significant others (WO), tingling or numbness (TI), voice concerns (VO), body image (BI), cramps (CR), dry mouth (DM), altered temperature tolerance (TO), impact on job or education (JE), joint pain (JP), and shoulder functioning (SH). The items of the C30 and the THY34 are transformed into scale scores ranging from 0 to 100, with higher values indicating a lower burden for functioning scales and higher burden for symptom scales [25]. Additionally, information on typical hypoparathyroid symptoms, such as tingling, cramps, or trousseau signs within the last 4 weeks, was obtained from the patient using a four-point Likert scale. Data on education, partnership, thyroxin intake, radioiodine treatment, calcium or vitamin D intake, and a previous diagnosis of hypoparathyroidism were obtained from the patient during the interview. Medical data such as histology, staging, date of diagnosis, type of surgery, and removal of parathyroid glands were obtained from the medical files of the

patient. The data for the general population were obtained from a dataset comprising the C30 scores of a representative sample of 2028 individuals from the German general population [26]. The sample can be assumed to be representative in respect to sociodemographic characteristics for the adult German population [26].

Statistical analysis

Patient characteristics were expressed as mean values (SD) for quantitative data or absolute and relative (%) frequencies for qualitative data. Univariate comparisons between participants and non-participants were performed using *t* tests, Mann-Whitney *U* tests, or chi^2 tests according to the distribution of the data. QOL scores for the C30 and the THY34 were calculated according to the official scoring manual of the EORTC [24]. Differences in QOL scores for gender, histology, and calcium or vitamin D intake were investigated using *t* tests, Mann-Whitney *U* tests, or chi^2 tests matching the distribution of the data.

For comparison of the C30 scores of the patients with a general population, the patients were categorized into having a worse or equal/better QOL score than the general population with similar age and gender distribution. Patients were defined as having worse QOL if their score was lower than the 25th quartile of the general population for functioning scales and if it was higher than the 75th quartile for symptom scales.

Descriptive statistics were used for describing the proportion of patients with worse QOL compared with the general population. We had access to the raw data.

Logistic regression was used to identify possible clinical or sociodemographic variables that might influence the odds of having a worse score than the general population. These variables were defined a priori based on the literature and clinical experience. The following variables were used in the model: age, time since surgery, gender, histology (DTC vs. medullary), education (up to 10 years vs. over 10 years), partnership (living with partner vs. living alone), and prolonged or ongoing calcium and vitamin D intake (yes vs. no).

This approach was chosen since the QOL scores of our sample did not meet the requirements for using multiple linear regression models due to the skewness of the QOL data.

Hypoparathyroid signs are presented descriptively using percentages. All statistical analyses were performed using R (R Version 3.2.4, R Foundation for statistical computing) [27].

Results

Patient characteristics

A total sample of 134 patients (31.8%) of all patients who had thyroid cancer surgery during the selected time frame (n = 421) fulfilled the inclusion criteria and were invited to participate in the study. The cohort included patients who underwent primary surgery or surgery for recurrent disease, occasionally with pre-existing hypoparathyroidisms. Of them, 75 patients (56.0%) participated in the study and were interviewed while 49 individuals (36.6%) did not reply to the invitation; seven patients (5.2%) were already deceased and three (2.2%) actively declined participation.

The sociodemographic and clinical characteristics are presented in Table 1. Of the 75 participants, 52 (69.3%) were female, and the mean age was 52.8 years (SD 15.9 years, range 20–88 years). The mean time since thyroid cancer surgery was 3.8 years (SD 1.6 years, range 1.2–6.7 years). Most patients were diagnosed with papillary thyroid cancer (61.3%), followed by medullary thyroid cancer (30.7%). Four patients (5.3%) were diagnosed with permanent hypoparathyroidism, of whom one participant was already diagnosed before thyroid cancer surgery, but 48% overall reported continued calcium and/or vitamin D intake. The reason for the intake of calcium and vitamin D was not assessed. There were no statistical significant differences between participants and non-participants regarding current age, time since surgery, gender, histology, UICC stage, type of surgery, and transplanted or removed parathyroid glands. Unfortunately, data on blood levels in the follow-up was available for only a small proportion of patients, despite the fact that such an analysis was offered to our patients. Therefore, assessment of the real frequency of permanent hypoparathyroidism was not possible. Data for the general population were available from 2028 individuals, with 56.1% of them being female with a mean age of 49.4 years (SD 17.2 years; range 16–92 years).

QOL in patients

The QOL scores of the patients are presented in Tables 2 and 3. Women reported worse scores regarding *appetite loss* compared with men (mean score 7.7 vs. 0; $p = 0.050$). Regarding other domains, no evidence of differences between women and men was observed. Patients with differentiated thyroid cancer (DTC) reported better *social functioning* than patients with medullary TC (mean score 91.7 vs. 78.3; $p = 0.018$). For all other functioning and symptom scales, no evidence of differences was observed regarding histology (DTC vs. medullary).

The highest scores in the THY34 were worry about significant others (mean 25.3; SD 27.4), thyroid fatigue (mean 21.9; SD 26.0), altered temperature tolerance (mean 20.1; SD 32.8), and joint pain (mean 20.0; SD 30.5). Almost no impairments were reported for swallowing (mean 2.7; SD 11.0), social support (mean 5.2; SD 11.5), body image (mean 5.3; SD 17.4), and impact on job or education (mean 5.8; SD 18.5). There was no evidence of differences in thyroid cancer–specific QOL between women and men and regarding histology (Tables 2 and 3).

Table 1 Sample characteristics at baseline and comparison with non-participants

	n (%)	*n* (%)		
	Whole sample (*n* = 134)	Participants (*n* = 75)	Non-participants (*n* = 59)	*p* value (participants vs. non-participants
Age at time of survey, years [mean (± SD)]	48.9 (15.7)	49.0 (15.9)	48.6 (15.6)	0.442
Time since surgery, years [mean (± SD)]	3.6 (1.6)	3.8 (1.6)	3.3 (1.5)	0.09
Gender				
Male	44 (32.8%)	23 (30.7%)	21 (35.6%)	0.676
Female	90 (67.2%)	52 (69.3%)	38 (64.4%)	
Education				
Below 10 years		11 (14.7%)		
10 years		21 (28.0%)		
Over 10 years		43 (57.3%)		
Partnership				
Partner		56 (74.7%)		
No partner		19 (25.3%)		
Histology				
Papillary	91 (67.9%)	46 (61.3%)	45 (76.3%)	0.088
Follicular	7 (5.2%)	3 (4.0%)	4 (6.8%)	
Medullary	30 (22.4%)	23 (30.7%)	7 (11.9%)	
Anaplastic	1 (0.7%)	0	1 (1.7%)	
Poorly differentiated	5 (3.7%)	3 (4.0%)	2 (3.4%)	
UICC stage				
Stage I	96 (71.6%)	51 (68.0%)	45 (76.3%)	0.298
Stage II	27 (20.1%)	15 (20.0%)	12 (20.3%)	
Stage III	3 (2.2%)	2 (2.7%)	1 (1.7%)	
Stage IV	8 (6.0%)	7 (9.3%)	1 (1.7%)	
Type of surgery				
Total thyroidectomy	125 (93.3%)	68 (90.7%)	57 (96.6%)	0.309
Partial/hemi thyroidectomy	9 (6.7%)	7 (9.3%)	2 (3.4%)	
Radioiodine treatment				
Never		24 (32.0%)		
Yes, more than 6 months ago		49 (65.3%)		
Yes, less than 6 months ago		2 (2.7%)		
Thyroxin intake (µg) [mean (± SD)]		136.6 (42.0)		
Current calcium and/or vitamin D intake				
Yes		36 (48.0%)		
No		39 (52.0%)		
Hypoparathyroidism				
Never		69 (92.0%)		
Transient		2 (2.7%)		
Permanent		4 (5.3%)		
Transplanted parathyroid glands				
0	23 (17.2%)	12 (16.0%)	11 (18.6%)	0.639
1	32 (23.9%)	19 (25.3%)	13 (22.0%)	
2	53 (39.6%)	32 (42.7%)	21 (35.6%)	
3	19 (14.2%)	8 (10.7%)	11 (18.6%)	
4	3 (2.2%)	1 (1.3%)	2 (3.4%)	
Unknown	4 (3.0%)	3 (4.0%)	1 (1.7%)	
Removed parathyroid glands				
0	117 (87.3%)	66 (88.0%)	51 (86.4%)	0.629
1	8 (6.0%)	3 (4.0%)	5 (8.5%)	
2	5 (3.7%)	3 (4.0%)	2 (3.4%)	
3	0	0	0	
4	0	0	0	
Unknown	4 (3.0%)	3 (4.0%)	1 (1.7%)	

t test for continuous data und chi-squared test for categorical data were used for the comparison of participants and non-participants

Patients who reported a current intake of calcium or vitamin D (vs. no intake) reported worse QOL in *global health* (mean score 68.5 vs. 76.7; $p = 0.041$), *physical functioning* (mean score 89.3 vs. 95.7; $p = 0.015$), *role functioning* (mean score 77.3 vs. 89.3; $p = 0.032$), and *joint pain* (mean score 29.6 vs. 11.1; $p = 0.009$).

Regarding hypoparathyroid symptoms, 32 patients (42.7%) reported tingling in the arms, legs, or face, 21

Table 2 Quality of life in patients with thyroid cancer and comparison between sexes

	Total (n = 75)	Male (n = 23)	Female (n = 52)	p value
EORTC QLQ-C30 functioning scales				
Global health (QL)	72.8 (15.9)	74.6 (16.2)	72.0 (20.9)	0.670
Physical functioning (PF)	92.6 (14.1)	94.8 (10.2)	91.7 (15.6)	0.853
Role functioning (RF)	83.6 (27.7)	90.6 (17.3)	80.4 (30.9)	0.335
Emotional functioning (EF)	78.9 (23.5)	82.2 (27.1)	77.4 (21.9)	0.170
Cognitive functioning (CF)	86.0 (22.8)	90.6 (22.4)	84.0 (22.9)	0.123
Social functioning (SF)	87.6 (24.8)	89.1 (23.4)	86.9 (25.6)	0.960
EORTC QLQ-C30 symptom scales				
Fatigue (FA)	26.1 (26.2)	20.8 (24.9)	24.9 (28.4)	0.206
Nausea and vomiting (NV)	1.6 (5.6)	0 (0)	2.2 (6.6)	0.094
Pain (PA)	15.6 (25.9)	18.8 (26.3)	14.1 (25.9)	0.291
Dyspnea (DY)	15.6 (29.2)	14.5 (24.3)	16.0 (31.3)	0.796
Insomnia (SL)	17.8 (30.7)	10.1 (25.5)	21.2 (32.4)	0.131
Appetite loss (AL)	5.3 (16.5)	0	7.7 (19.4)	0.050
Constipation (CO)	4.0 (13.4)	2.9 (13.9)	4.5 (13.2)	0.362
Diarrhea (DI)	5.3 (17.4)	5.8 (21.7)	5.1 (15.3)	0.756
Financial difficulties (FI)	6.2 (18.7)	10.1 (25.5)	4.5 (14.8)	0.328
EORTC QLQ-THY34 symptom scales				
Discomfort in the head and neck (DN)	11.7 (17.1)	11.1 (16.1)	12.0 (17.7)	0.934
Thyroid fatigue (FA_THY)	21.9 (26.0)	16.4 (25.5)	24.4 (26.1)	0.148
Fear (FE)	13.0 (15.4)	12.1 (14.6)	13.5 (15.9)	0.721
Hair problems (HA)	12.2 (25.6)	9.4 (25.0)	13.5 (26.0)	0.281
Restlessness (RE)	18.2 (24.4)	12.3 (21.4)	20.8 (25.3)	0.117
Social support (SO)	5.2 (11.5)	4.8 (11.0)	5.3 (11.7)	0.993
Swallowing (SW)	2.7 (11.0)	1.4 (7.0)	3.2 (12.4)	0.595
Worry about important others (WO)	25.3 (27.4)	21.7 (26.9)	26.9 (27.7)	0.401
Tingling or numbness (TI)	14.9 (20.4)	18.1 (19.4)	13.5 (20.9)	0.247
Voice concerns (VO)	8.7 (14.3)	9.2 (14.5)	8.5 (14.4)	0.722
Body image (BI)	5.3 (17.4)	4.3 (11.5)	5.8 (19.5)	0.739
Cramps (CR)	12.9 (28.4)	8.7 (20.6)	14.7 (31.3)	0.610
Dry mouth (DM)	16.0 (30.2)	13.0 (24.1)	17.3 (32.7)	0.886
Altered temperature tolerance (TO)	20.1 (32.8)	14.5 (28.1)	23.7 (34.5)	0.306
Impact on job or education (JE)	5.8 (18.5)	8.7 (23.0)	4.5 (16.2)	0.452
Joint pain (JP)	20.0 (30.5)	26.1 (38.9)	17.3 (26.0)	0.642
Shoulder function (SH)	7.1 (22.1)	5.8 (21.7)	7.7 (22.5)	0.582

Functioning scales: A higher score is indicating a better QOL. Symptom scales: A lower scores is indicating fewer problems. Mann-Whitney U test was used for the comparison (male vs. female)

(28.0%) had unexplainable irritability or feelings of anxiety, 15 (20.0%) had painful cramps in the hands or feet, 10 (13.3%) respiratory distress, 6 (8.0%) heart trouble, and one (1.3%) had had laryngeal cramps within the last 4 weeks. No patient reported trousseau signs of tetany or cramps while measuring blood pressure within the last 4 weeks. There was no significant difference in patients with current calcium and vitamin D intake and patients with no intake regarding hypoparathyroid symptoms.

QOL compared with the general population

Table 4 presents the number and percentage of patients who reported worse C30 scores compared with the age- and sex-adjusted general population. High percentages of worse QOL scores compared with the general population were seen in the following domains: *fatigue* (42.7%), *emotional functioning* (33.3%), *cognitive functioning* (30.7%), *pain* (28.0%), *insomnia* (28.0%), *dyspnea* (26.7%), *role functioning* (26.7%), and *social functioning* (26.7%).

Table 3 Quality of life in patients with different histologies and current vs. no calcium or vitamin D intake

	DTC ($n = 52$)	Medullary TC ($n = 23$)	p value	Current calcium or vitamin D intake ($n = 36$)	No calcium or vitamin D intake ($n = 39$)	p value
EORTC QLQ-C30 functioning scales						
Global health (QL)	73.2 (20.2)	71.7 (18.4)	0.700	68.5 (17.4)	76.7 (20.8)	0.041
Physical functioning (PF)	93.6 (13.5)	90.4 (15.7)	0.116	89.3 (16.2)	95.7 (11.3)	0.015
Role functioning (RF)	86.2 (25.9)	77.5 (31.2)	0.139	77.3 (30.9)	89.3 (23.4)	0.032
Emotional functioning (EF)	77.7 (25.2)	81.5 (19.6)	0.795	77.5 (22.5)	80.1 (24.7)	0.461
Cognitive functioning (CF)	85.3 (24.8)	87.7 (17.6)	0.849	87.0 (20.4)	85.0 (25.0)	0.956
Social functioning (SF)	91.7 (20.5)	78.3 (31.2)	0.018	84.7 (25.3)	90.2 (24.4)	0.119
EORTC QLQ-C30 symptom scales						
Fatigue (FA)	26.1 (26.5)	26.1 (26.3)	0.925	29.3 (25.2)	23.1 (27.1)	0.166
Nausea and vomiting (NV)	1.9 (6.3)	0.7 (3.5)	0.441	1.9 (6.6)	1.3 (4.5)	0.901
Pain (PA)	15.4 (25.5)	15.9 (27.3)	0.901	20.4 (28.8)	11.1 (22.4)	0.124
Dyspnea (DY)	15.4 (29.1)	15.9 (29.9)	0.999	22.2 (33.8)	9.4 (22.9)	0.063
Insomnia (SL)	17.9 (29.9)	17.4 (33.1)	0.780	25.9 (35.7)	10.3 (23.1)	0.047
Appetite loss (AL)	5.8 (17.1)	4.3 (15.3)	0.723	7.4 (18.0)	3.4 (14.9)	0.130
Constipation (CO)	5.1 (15.3)	1.4 (7.0)	0.322	2.8 (9.3)	5.1 (16.3)	0.737
Diarrhea (DI)	6.4 (19.8)	2.3 (9.6)	0.676	4.6 (14.1)	6.0 (20.0)	0.953
Financial difficulties (FI)	4.5 (16.2)	10.1 (23.4)	0.105	7.4 (19.7)	5.1 (18.0)	0.288
EORTC QLQ-THY34 symptom scales						
Discomfort in the head and neck (DN)	11.7 (18.2)	11.6 (14.8)	0.602	9.9 (11.8)	13.4 (20.9)	0.847
Thyroid fatigue (FA_THY)	22.6 (26.7)	20.3 (25.0)	0.842	22.5 (22.5)	21.4 (29.2)	0.356
Fear (FE)	13.5 (15.9)	12.1 (14.6)	0.957	11.1 (12.7)	14.8 (17.5)	0.554
Hair problems (HA)	12.5 (25.1)	11.6 (27.3)	0.581	12.5 (25.9)	12.0 (25.6)	0.897
Restlessness (RE)	18.9 (24.9)	16.7 (23.6)	0.699	20.4 (23.6)	16.2 (25.2)	0.262
Social support (SO)	4.9 (11.3)	5.8 (12.0)	0.580	6.5 (12.6)	4.0 (10.4)	0.227
Swallowing (SW)	3.8 (13.0)	0 (0)	0.130	3.7 (13.9)	1.7 (7.4)	0.573
Worry about important others (WO)	26.6 (27.9)	22.5 (26.4)	0.753	23.4 (22.8)	27.1 (31.2)	0.906
Tingling or numbness (TI)	17.6 (22.0)	8.7 (15.0)	0.116	19.0 (21.5)	11.1 (18.7)	0.064
Voice concerns (VO)	9.6 (14.9)	6.8 (12.9)	0.255	7.4 (12.7)	10.0 (15.7)	0.412
Body image (BI)	6.4 (19.8)	2.9 (9.6)	0.676	2.8 (9.3)	7.7 (22.2)	0.482
Cramps (CR)	14.7 (29.8)	8.7 (15.0)	0.336	11.1 (28.7)	14.5 (28.4)	0.291
Dry mouth (DM)	18.6 (32.6)	10.1 (23.4)	0.281	15.7 (29.3)	16.2 (31.4)	0.961
Altered temperature tolerance (TO)	20.5 (31.8)	21.7 (35.7)	0.923	20.4 (32.1)	21.4 (33.8)	0.954
Impact on job or education (JE)	4.5 (16.2)	8.7 (23.0)	0.452	5.6 (18.7)	6.0 (18.5)	0.809
Joint pain (JP)	19.9 (29.0)	20.3 (34.4)	0.737	29.6 (34.5)	11.1 (23.4)	0.009
Shoulder function (SH)	4.5 (17.5)	13.0 (29.7)	0.090	7.4 (19.7)	6.8 (24.4)	0.297

Functioning scales: A higher score is indicating a better QOL. Symptom scales: A lower scores is indicating fewer problems. Mann-Whitney U test was used for the comparisons (DTC vs. medullary TC and current calcium vs. no calcium)

Determinants of worse QOL domains compared with the general population

Current calcium or vitamin D intake (vs. no intake) had a significant effect on the odds of having a worse QOL compared with the general population in *role functioning* (OR 4.63; 95% CI 1.28–19.77) and *emotional functioning* (OR 3.87; 95% CI 1.11–15.42) (Table 5).

Age (as a continuous variable) was associated with *global health* (OR 0.94; 95% CI 0.89–0.99) and *cognitive functioning* (OR 0.94; 95% CI 0.89–0.98).

Higher education of more than 10 years of schooling (vs. ≤ 10 years of schooling) was associated with *emotional functioning* (OR 0.21; 95% CI 0.05–0.71).

Living with a partner (vs. living alone) was associated with *physical functioning* (OR 0.19; 95% CI 0.03–0.97).

Table 4 Proportion of worse QOL in thyroid cancer patients compared with age- and sex-adjusted general population

	Worse score, *n* (%)
EORTC QLQ-C30 functioning scales	
Global health (QL)	14 (18.7%)
Physical functioning (PF)	12 (16.0%)
Role functioning (RF)	20 (26.7%)
Emotional functioning (EF)	25 (33.3%)
Cognitive functioning (CF)	23 (30.7%)
Social functioning (SF)	20 (26.7%)
EORTC QLQ-C30 symptom scales	
Fatigue (FA)	32 (42.7%)
Nausea and vomiting (NV)	6 (8.0%)
Pain (PA)	21 (28.0%)
Dyspnea (DY)	20 (26.7%)
Insomnia (SL)	21 (28.0%)
Appetite loss (AL)	8 (10.7%)
Constipation (CO)	7 (9.3%)
Diarrhea (DI)	8 (10.7%)
Financial difficulties (FI)	9 (12.0%)

Worse QOL: Patients were appointed a worse score if their personal score was lower than the 25th quartile of the age- and sex-adjusted general population for functioning scales and if it was higher than the 75th quartile for symptom scales

Discussion

Our study shows that patients more than 1 year post surgery who had early postoperatively low calcium or PTH levels report reduced QOL in several domains compared with an age- and sex-adjusted general population. Additionally, our study showed that almost half of the patients reported the intake of calcium or vitamin D and that intake was associated with higher odds for worse QOL in several domains.

Thirty-two percent of all patients who had thyroid cancer surgery during the selected time frame had low calcium or PTH levels within 24 h after surgery and 56% of those participated in the study. Forty-eight percent of these patients were currently still on calcium and vitamin D supplementation, which represents 8.6% of the patients who underwent thyroid cancer surgery. In a large survey among participants of a thyroid cancer self-help organization in 2010, 13.8% reported low calcium levels 1 year after diagnosis [28]. In a recent survey by the German self-help organization "LebenOhneSchilddrüse e.V.," 19.4% of the participants reported low serum calcium levels 1 year after diagnosis (LebenOhneSchilddrüse e.V., data not published). This shows that patients still have problems with their calcium levels long after TC surgery. McIntyre et al. [29] reported that 29% of patients required a combination of calcium and vitamin D supplementation 6 months after TC diagnosis. Aschebrook-Kilfoy et al. [30] consider that the rates of hypocalcemia and therefore HPT might be higher than expected by the literature.

Regarding a reduced QOL in TC patients at a minimum of 1 year post diagnosis, our results are in line with the current literature [8–10], although other studies showed a similar QOL compared with a general population [31, 32], indicating that QOL may also improve with time since surgery. These findings could not be confirmed by our study, with time since surgery showing no significant improvements in QOL domains. For symptom domains, our results are also in accordance with the current literature; causes of the most problems for thyroid cancer survivors are fatigue, pain, dyspnea, and insomnia [6, 8].

The most frequent thyroid cancer–specific problems identified in our study were *worry about significant others*, *altered temperature tolerance*, *joint pain*, and *thyroid fatigue*. Some of these symptoms have also been identified by others as among the most troubling thyroid cancer–specific symptoms [9, 27, 28, 33]. While other studies also report problems related to fear of recurrence and lacking social support [10, 29, 34, 35], our participants reported few problems in these domains. In a study by Schultz et al. [36], 43.4% of thyroid cancer survivors stated that having cancer improved their family relationships, while only 11.6% reported that it damaged their family relationship, with the remaining patients reporting no changes or mixed effects.

In our study, patients who reported a continued calcium or vitamin D intake had worse QOL scores for *global health*, *physical functioning*, *role functioning*, and *insomnia* compared with patients without current calcium or vitamin D intake. Additionally, current calcium or vitamin D intake was associated with higher odds of having worse QOL in the *role functioning* and the *emotional functioning* domains of the C30 compared with the general population. The effect of current calcium or vitamin D intake on QOL domains might have two possible reasons. On the one hand, there is the possibility that the number of patients with hypoparathyroidism in the group with current calcium and vitamin D intake is actually higher than what we found. In our study, a subgroup of patients reported typical hypoparathyroid symptoms, such as tingling in the arms, legs, or face (42.7%), unexplainable irritability or feelings of anxiety (28%), or painful cramps in the hands or feet (20%), all within the last 4 weeks. Therefore, there is the possibility that the number of patients with permanent HPT in our sample may be higher than reported. HPT patients have a reduced QOL [22]; however, the cause of this may not only be due to hypocalcemia but also to PTH deficiency directly. Previous studies have reported that PTH receptors exist in several brain regions, the central nervous system, and muscle cells [37–40], and a lack of PTH might therefore explain reduced QOL in domains related to mental or

Table 5 Predictors of having worse QOL in thyroid cancer patients compared with an age- and sex-adjusted general population (multiple logistic regression)

EORTC QLQ-C30 functioning scales						
Independent variables (reference)	Global health	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Age	0.94* [0.89; 0.99]	0.99 [0.95; 1.04]	0.99 [0.94; 1.03]	0.96 [0.92; 1.00]	0.94* [0.89; 0.98]	0.97 [0.93; 1.01]
Time since surgery	1.06 [0.69 ; 1.65]	1.04 [0.66; 1.64]	1.02 [0.70; 1.48]	0.91 [0.63; 1.30]	0.91 [0.62; 1.31]	0.91 [0.63; 1.29]
Female gender (male)	2.50 [0.46; 21.86]	4.01 [0.71; 36.81]	2.75 [0.68; 13.81]	1.42 [0.38; 5.76]	2.76 [0.65; 15.28]	0.89 [0.24; 3.51]
Over 10 years of schooling (≤ 10 years of schooling)	0.29 [0.06; 1.31]	0.70 [0.14; 3.49]	0.77 [0.20; 2.88]	0.21* [0.05; 0.71]	0.41 [0.11; 1.42]	0.50 [0.14; 1.74]
Living with partner (living alone)	0.26 [0.05; 1.30]	0.19* [0.03; 0.97]	0.38 [0.09; 1.49]	0.42 [0.11; 1.57]	0.49 [0.12; 2.00]	0.49 [0.13; 1.81]
Current calcium or vitamin D intake (no intake)	2.89 [0.62; 15.63]	4.81 [0.93; 34.18]	4.63* [1.28; 19.77]	3.87* [1.11; 15.42]	1.76 [0.48; 6.86]	2.05 [0.59; 7.67]
Medullary thyroid cancer (differentiated thyroid cancer)	0.68 [0.11; 3.33]	0.84 [0.16; 3.99]	1.38 [0.37; 4.98]	0.59 [0.15; 2.13]	1.66 [0.43; 6.61]	2.65 [0.73; 9.76]
EORTC QLQ-C30 symptom scales						
	Fatigue	Pain	Dyspnea	Insomnia		
Age	0.96 [0.92; 1.00]	1.01 [0.97; 1.05]	1.03 [0.99; 1.07]	1.00 [0.96; 1.04]		
Time since surgery	1.07 [0.76; 1.50]	1.15 [0.79; 1.69]	1.25 [0.86; 1.86]	1.06 [0.74; 1.53]		
Female gender (male)	2.06 [0.61; 7.48]	0.40 [0.10; 1.48]	0.93 [0.26; 3.54]	2.04 [0.55; 8.93]		
Over 10 years of schooling (≤ 10 years of schooling)	0.79 [0.25; 2.44]	0.42 [0.12; 1.48]	0.87 [0.24; 3.23]	0.47 [0.13; 1.61]		
Living with partner (living alone)	0.71 [0.21; 2.41]	1.77 [0.47; 7.82]	0.73 [0.20; 2.71]	0.79 [0.21; 3.11]		
Current calcium or vitamin D intake (no intake)	2.33 [0.75; 7.85]	3.08 [0.94; 11.01]	3.06 [0.92; 11.20]	2.93 [0.87; 10.83]		
Medullary thyroid cancer (differentiated thyroid cancer)	0.84 [0.25; 2.80]	0.34 [0.08; 1.28]	0.47 [0.11; 1.76]	0.71 [0.18; 2.51]		

Odds ratio for having worse QOL than the age- and sex-adjusted general population (confidence interval). Domains were included if a relevant number of participants had a lower score compared with general population

*Statistically significant

physical health independent of hypocalcemia status. On the other hand, we cannot exclude that some patients are overtreated with calcium or vitamin D without indication. This might lead to short- or long-term complications of calcium or vitamin D intake [19–21], which leads to reduced QOL. Unfortunately, we did not have data on current blood levels for all patients, so we could not determine current calcium and PTH status to identify HPT or overtreated patients. Another factor in our study that was associated with higher odds of having good QOL in a few domains was higher education. The influence of education on QOL remains controversial in the literature. While some studies have found a positive effect on QOL [9, 36], others have found no association [41, 42]. If higher education is assumed to have a positive effect on QOL, our study might have underestimated the QOL impairments since we included had a high proportion of highly educated patients. Another point, which requires consideration when looking at thyroid cancer patients QOL, is the potential difference between patient and physician perception of these impairments because this can lead to miscommunication between patient and physician. A study by James et al. [43] found that medical physicians overestimate the decrease in QOL of patients while surgeons seemed to evaluate them more accurately. Nevertheless, both groups significantly underestimated the prevalence of physical symptoms, like hypocalcemia, compared with the patients' perception. This highlights the point that focus also needs to be set to the postsurgical complications like hypocalcemia or vocal cord palsy.

Our study has several limitations. Firstly, because of its cross-sectional design, the obtained QOL can only be considered as a snapshot of the patients' QOL. It is not unlikely that patients with good QOL participated more often than patients with worse QOL, thereby introducing a selection bias. Our sample does not represent the typical TC patient population due to the inclusion criteria and the high proportion of medullary TCs. There was no assessment of comorbidities in our patient population; however, the effect of comorbidities on QOL is as yet controversial [8–10]. Additionally, since our sample size is quite small, it was difficult to detect small differences.

One strength of our study was that we used thyroid cancer-specific questionnaires to assess the patients' QOL. This gave us the opportunity to assess thyroid cancer–related QOL impairments, which could be missed if a generic questionnaire were used. Another strength of our study was that we obtained information on continued calcium or vitamin D intake and on whether the patients were diagnosed with permanent HPT; this is important because hypoparathyroidism is associated with worse QOL [22].

It has been shown that a high proportion of patients still report calcium or vitamin D intake even 1 year after diagnosis without being diagnosed for HPT. This may imply that HPT in Germany is not adequately evaluated or that treatment with calcium or vitamin D is not stopped even when the intake is no longer necessary. Both of these possible explanations, a high rate of undiagnosed HPT or unnecessary calcium or vitamin D intake, might negatively influence the long-term QOL of TC survivors.

Conclusions

This study has also shown that patients at 1 year and more post surgery report impairments in QOL. Further studies should especially focus on surgical complications such as HPT and vocal cord palsy and their effects on QOL.

Author contribution All authors contributed to the conception and design of the study. All authors participated in drafting or critically revising the manuscript, and all authors' approved the final version of the manuscript for submission.

Matthias Büttner and Thomas Musholt contributed to the acquisition and interpretation of data.

Matthias Büttner contributed to the analysis of the data.

Matthias Büttner will use this paper for his PhD thesis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures involving human participants in this study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This study was approved by the Ethics-Committee of the Landesärztekammer Rhineland-Palatinate (# 837.238.16).

Informed consent Informed consent was obtained from all individual participants included in the study.

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8.2 Büttner et al. (2020) - Quality of life in patients with hypoparathyroidism after treatment for thyroid cancer

Zusammenfassung

Einleitung: Chirurgische Komplikationen wie Hypoparathyreoidismus (hypoPT) oder Stimmbandlähmung werden selten berücksichtigt, wenn die Lebensqualität (LQ) von Patienten mit Schilddrüsenkrebs untersucht wird. Ziel dieser Studie war es, den Unterschied in der Lebensqualität von Überlebenden von Schilddrüsenkrebs mit und ohne hypoPTzu messen.

Methoden: Potenzielle Teilnehmer für die Analyse kamen aus einer Studie, in der ein Schilddrüsenkrebs-spezifisches Lebensqualitätsinstrument validiert wurde. Sie wurden in die Analyse eingeschlossen, wenn bei ihnen mindestens neun Monate zuvor Schilddrüsenkrebs diagnostiziert worden war. Die Lebensqualität wurde mithilfe des EORTC QLQ-C30 und einiger hypoPT spezifischen Symptomen (z. B. Kribbeln in Fingern oder Zehen) gemessen. Der hypoPT-Status und andere klinische Daten wurden aus den Patientenakten extrahiert. Vergleiche der Lebensqualitätsskalen zwischen Patienten mit und ohne hypoPT wurden mithilfe des Mann-Whitney-U-Tests durchgeführt. Das Auftreten hypoPT-bedingter Symptome wurde mittels Chi-Quadrat-Tests verglichen. Es wurde eine multiple ordinale Regressionsanalyse durchgeführt, um Faktoren zu identifizieren, die einen Einfluss auf die Lebensqualität haben könnten.

Ergebnisse: Bei 17 der 89 auswertbaren Patienten wurde permanenter Hypoparathyreoidismus diagnostiziert. Patienten mit hypoPT hatten, im Vergleich zu Patienten ohne hypoPT, eine statistisch signifikant reduzierte Lebensqualität in neun von 15 Skalen des EORTC QLQ-C30. Die Regressionsanalyse zeigte, dass hypoPT negativ mit verschiedenen Skalen EORTC QLQ-C30 assoziiert war. Patienten mit und ohne hypoPT zeigten eine hohe Prävalenz an typischen hypoPT Symptomen.

Fazit: Schilddrüsenkrebspatienten mit postoperativem permanenten hypoPT berichten Lebensqualitätseinschränkungen im Vergleich zu Patienten ohne hypoPT. Der Einfluss von hypoPT auf die Lebensqualität sollte berücksichtigt werden, wenn der Lebensqualität von Schilddrüsenkrebspatienten gemessen wird.

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Quality of Life in Patients With Hypoparathyroidism After Treatment for Thyroid Cancer

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Abbreviations: CRF, case report form; EORTC, European Organisation for Research and Treatment of Cancer; HPT, hypoparathyroidism; PTH, parathyroid hormone; QLQ-C, Quality of Life Questionnaire Core; QOL, quality of life; TKI, tyrosine kinase inhibitor; UICC, Union for International Cancer Control TNM Classification.

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Abstract

Purpose: Surgical complications such as hypoparathyroidism (HPT) or vocal cord palsy are seldom assessed when the quality of life (QOL) in thyroid cancer patients is investigated.

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The aim of this study was to measure the QOL difference in thyroid cancer survivors with and without HPT.

Methods: Participants for this analysis were enrolled in 13 countries from a study that pilot-tested a thyroid cancer–specific QOL instrument. They were included if they had been diagnosed with thyroid cancer at least 9 months previously. QOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) and some items on HPT symptoms (eg, tingling in fingers or toes). HPT status and other clinical data were extracted from the patients' medical charts. Comparisons of QOL domains between patients with and without HPT were performed using Mann-Whitney *U* test. The occurrence of HPT-related symptoms was compared using chi-square tests. Multiple ordinal regression analysis was performed to evaluate factors that might affect QOL.

Results: Eighty-nine patients participated in this study, 17 of whom were considered to have HPT. Patients in the HPT group reported significantly reduced QOL in 9 of the 15 scales of the EORTC QLQ-C30 compared to patients without HPT. Regression analysis showed that HPT was independently negatively associated with various scales of the QLQ-C30. Both groups showed a high prevalence of typical HPT symptoms.

Conclusion: Thyroid cancer patients with HPT report significantly impaired QOL compared to thyroid cancer survivors without HPT. The assessment of HPT should be considered when measuring QOL in thyroid cancer patients.

Freeform/Key Words: hypoparathyroidism, thyroid cancer, quality of life, well-being

Hypoparathyroidism (HPT) is an orphan endocrine disorder and is defined by hypocalcemia due to absent or low levels of parathyroid hormone (PTH), often accompanied by hyperphosphatemia (1, 2). The current treatment for HPT consists of calcium and vitamin D supplementation because HPT is currently the only endocrine disorder for which replacing the missing hormone as a standard therapeutic option is not possible (2). Recent studies show promising results using synthetic PTH as treatment, but this treatment option is approved only for patients whose hypocalcemia is inadequately controlled with calcium and activated vitamin D (3, 4).

Little is known about the prevalence of HPT. Studies from the United States (5) and Norway (6) respectively report a prevalence of 37 per 100 000 and 9.4 per 100 000 inhabitants. A Danish registry-based study found a prevalence of 24 cases per 100 000 inhabitants, with 22 per 100 000 due to surgery and 2 per 100 000 stemming from nonsurgical reasons (7, 8). The differences in the prevalence may be explained by different definitions of HPT and different time frames when HPT is considered to be permanent (9, 10). It is estimated that 30% to 40% of surgical HPT is related to thyroid cancer or other malignancies (7, 11, 12). Only a few studies with heterogeneous HPT populations have investigated the quality of life (QOL) in patients with HPT (3, 6, 11, 13-16). All studies found a reduced QOL in HPT patients using generic QOL instruments (17). However, it cannot be ruled out that some of the QOL impairments may be due to the underlying disease itself and not to HPT since, for example, thyroid cancer patients without HPT also report a reduced QOL even long after surgery (18, 19). Nevertheless, it is possible that the findings of reduced QOL in thyroid cancer survivors might be due to impairments related to HPT (20). Therefore, the aim of this study was to assess the QOL differences between HPT and non-HPT patients after a minimum of 9 months after the thyroid cancer diagnosis using a disease-specific cancer instrument and to assess whether differences in typical HPT symptoms, like pain in the joints, tingling or numbness in fingers or toes, exist between the 2 groups.

Materials and Methods

Design

This analysis results from an international cross-sectional study aimed to pilot-test a thyroid cancer–specific QOL instrument (21). Patients were interviewed between January 2015 and January 2016. In this study, the HPT status of the patients was documented by answering the question regarding parathyroid insufficiency on the case report form (CRF) with the original data being extracted from the patients' medical record, which made it possible for these data to be used for our present research question.

Patients were enrolled consecutively from 14 centers when the following inclusion criteria were fulfilled: (i) histologically verified thyroid cancer, (ii) treatment for thyroid cancer, (iii) ability to understand and complete the questionnaire, (iv) age 18 years or older, and (v) written informed consent.

Patients were included in this analysis if clear information on parathyroid status was available. Thyroid cancer patients for this analysis were defined as having HPT if they were more than 9 months postdiagnosis and they had a current parathyroid insufficiency at the time of interview. Parathyroid insufficiency was recorded in the CRF as "yes," "no," or "unknown." The group defined as having no HPT consisted of thyroid cancer patients more than 9 months postdiagnosis with no current parathyroid insufficiency. Patients with unknown HPT status or fewer than 9 months postdiagnosis were excluded from this analysis because it would not be clear whether their HPT was transient or permanent. The period of 9 months was chosen to ensure that patients were at least 6 months postsurgical treatment for thyroid cancer and that HPT can be considered permanent. According to Dionigi et al (22), the time between diagnosis of thyroid cancer and the surgical treatment of the disease ranges from 7 to 30 days. The guidelines for the management of thyroid cancer by the British Thyroid Association state that the time from the general practitioner referral to surgery for thyroid cancer should not exceed 62 days (23). Therefore, we assume that all patients in our study received their treatment for thyroid cancer within 3 months postdiagnosis and have had HPT for at least 6 months using the 9-month time frame for inclusion.

Assessments

All patients completed a cancer-specific QOL questionnaire, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) (24). The EORTC QLQ-C30 is a tool specifically developed for assessing the QOL of cancer patients and used in various studies. It consists of 30 items summarized into 5 functioning scales (physical functioning [PF], role functioning [RF], emotional functioning [EF], cognitive functioning [CF], social functioning [SF], 1 global quality of life [QL] scale) and 9 symptom scales (fatigue [FA], nausea and vomiting [NV], pain [PA], dyspnea [DY], insomnia [SL], appetite loss [AL], constipation [CO], diarrhea [DI], and financial difficulties [FI]) (24). The items of the EORTC QLQ-C30 (4-point-Likert scale questions: "not at all," "a bit," "quite a bit," and "very much") were summarized into scales and transformed to scores ranging from 0 to 100, with higher values indicating lower impairments in functioning scales and a greater degree of impairments in symptom scales (25).

Questions on HPT symptoms were added, using the same 4-point Likert-scale as response categories ("not at all," "a bit," "quite a bit," and "very much"). The questions related to attacks of tiredness, restlessness or agitation, pain in the joints, tingling or numbness in fingers or toes, tingling or numbness around the mouth, muscle cramps, and rapid heartbeat. The questions regarding HPT symptoms were selected from the module under development according to findings from the literature (3, 6, 11, 13-16).

Information on clinical characteristics (eg, tumor stage, histology, type of surgery, and parathyroid insufficiency) was obtained from the CRF, which was extracted from the patients' medical charts. All participants gave written informed consent, and all procedures were performed in accordance with the ethical standards of the Declaration of Helsinki and the local ethics committees. Ethical approval for the principal investigator was granted December18, 2014 (No. 837.470.14.9709).

Statistical analysis

QOL scores for the QLQ-C30 were calculated according to the official scoring manual of the EORTC (25). The HPT symptoms were treated as single items and not combined into a scale.

Descriptive statistics of the study population are given as mean values or percentages depending on the type of data. Post hoc power calculation showed that there was a power above 80% to detect a large effect size given the used samples and an α level of .05.

Univariate comparisons between the characteristics of the HPT and the non-HPT patients were performed using *t* tests or Mann-Whitney *U* tests for continuous data depending on the distribution of the data and chi-square tests for categorical variables.

Differences in QOL (as measured with the QLQ-C30) between the HPT and the non-HPT patients were determined using the Mann-Whitney *U* tests because of the distribution of the data.

Multiple ordinal regression analysis was performed to evaluate factors that might affect QOL scales. The nausea and vomiting scale was excluded from regression analysis because of too few reported problems. Ordinal regression was performed using the MASS-package in R. Symptoms of HPT were analyzed descriptively using percentages; the chi-square test was applied for the comparison of symptoms between HPT patients and non-HPT patients.

Results

Study characteristics

Of the 182 participants in the study, 91 (50%) fulfilled the inclusion criteria for the analysis. Seventeen (19%) of the included participants had parathyroid insufficiency, 72 (79%) had no parathyroid insufficiency, and in 2 (2%) the HPT status was unknown. There were no significant differences in age (54.5 years vs 52.4 years, $P = .5$), sex (26% male vs 18% male, $P = .6$), and other sociodemographic or clinical characteristics between the HPT and the non-HPT group (Table 1).

Table 1. Characteristics of the study population

Characteristic	All (n = 89)	HPT (n = 17)	Non-HPT (n = 72)	*P* (HPT vs non-HPT)
Age, SD	54.5 (16.1)	52.4 (16.7)	55.0 (16.1)	.51
Sex				.58
Male	25.8% (23)	17.6% (3)	37.7% (20)	
Female	74.2% (66)	82.4% (14)	62.3% (52)	
Time since diagnosis, SD, y	5.9 (8.3)	7.1 (6.6)	5.7 (8.7)	.33
Range	0.77-53.4	0.77-19.4	0.82-53.4	
Education				.11
Compulsory or less	32.6% (29)	52.9% (9)	27.8% (20)	
Postcompulsory	36.0% (32)	23.5% (4)	38.9% (28)	
University degree	28.1% (25)	17.6% (3)	30.6% (22)	
Unknown	3.4% (3)	5.9% (1)	2.8% (2)	
Histology				.45
Follicular	13.5% (12)	5.9% (1)	15.3% (11)	
Papillary	67.4% (60)	82.4% (14)	63.9% (46)	
Medullary	14.6% (13)	11.8% (2)	15.3% (11)	
Other	4.5% (4)	0	5.6% (4)	
T				.27
T1	22.5% (20)	17.6% (3)	23.6% (17)	
T2	15.7% (14)	5.9% (1)	18.1% (13)	
T3	28.1% (25)	29.4% (5)	27.8% (20)	
T4a	13.5% (12)	11.8% (2)	13.9% (10)	
T4b	2.2% (2)	0	2.8% (2)	
Tx	15.7% (14)	35.3% (6)	11.1% (8)	
Unknown	2.2% (2)	0	2.8% (2)	
N				.35
N0	37.1% (33)	17.6% (3)	41.7% (30)	
N1a	14.6% (13)	17.6% (3)	13.9% (10)	
N1b	22.5% (20)	29.4% (5)	20.8% (15)	
Nx	23.6% (21)	35.3% (6)	20.8% (15)	
Unknown	2.2% (2)	0	2.8% (2)	
M				.12
M0	67.4% (60)	47.1% (8)	72.2% (52)	
M1	23.6% (21)	41.2% (7)	19.4% (14)	
Mx	9.0% (8)	11.8% (2)	8.3% (6)	
UICC, 8th ed				.44
I	47.2% (42)	29.4% (5)	51.4% (37)	
II	18.0% (16)	23.5% (4)	16.7% (12)	
III	5.6% (5)	5.9% (1)	5.6% (4)	
IV	16.9% (15)	29.4% (5)	13.9% (10)	
Unknown	12.4% (11)	11.8% (2)	12.5% (9)	
Karnofsky Performance Status				.09
< 70	3.4% (3)	11.8% (2)	1.4% (1)	
≥ 70	95.5% (85)	88.2% (15)	97.2% (70)	
Unknown	1.1% (1)	0	1.4% (1)	
Type of surgery				.89
Hemithyroidectomy	5.6% (5)	5.9% (1)	5.6% (4)	
Partial thyroidectomy	1.1% (1)	0	1.4% (1)	
Total thyroidectomy	93.3% (83)	94.1% (16)	93.1% (67)	
Neck dissection				.18
No	39.3% (35)	23.5% (4)	43.1% (31)	
Yes	57.3% (51)	76.5% (13)	52.8% (38)	
Unknown	3.4% (3)	0	4.2% (3)	
Vocal cord impairment due to surgery				.87
No	77.5% (69)	76.5% (13)	77.8% (56)	
Yes	21.3% (19)	23.5% (4)	20.8% (15)	
Unknown	1.1% (1)	0	1.4% (1)	

Univariate comparisons between the characteristics of the HPT and the non-HPT patients were performed using *t* tests or Mann-Whitney *U* tests for continuous data depending on the distribution of the data and chi-square tests for categorical variables.

Abbreviations: HPT, hypoparathyroidism; UICC, Union for International Cancer Control TNM Classification.

At the time of the interview, no participants were undergoing radioactive iodine, whereas 4 (24%) participants in the HPT group and 6 (8%) participants in the non-HPT group received their last radioactive iodine treatment within the previous 6 months. Two participants (3%) in the non-HPT group were currently receiving chemotherapy; no participants in the HPT group were undergoing chemotherapy. For participants undergoing treatment with tyrosine kinase inhibitors (TKIs), 3 (18%) were in the HPT group, and 6 (8%) were in the non-HPT group.

Quality of life in patients with and without hypoparathyroidism after thyroid cancer

The results for QOL and the comparisons between participants with HPT and without HPT are presented in Table 2. Participants with HPT scored significantly worse in 5 out of 6 functioning scales of the QLQ-C30 compared to patients without HPT. Global health (51.0 vs 68.5, $P = .03$), physical functioning (66.7 vs 82.7, $P = .007$), role functioning (66.7 vs 82.7, $P = .002$), emotional functioning (56.9 vs 80.0, $P = .004$), and social functioning (69.6 vs 86.0, $P = .004$) were significantly lower, whereas cognitive functioning (71.6 vs 83.1, $P = .06$) was not significantly decreased. Furthermore, HPT patients scored significantly worse on the symptom scales for fatigue (45.8 vs 28.7, $P = .04$), pain (41.2 vs 17.6, $P = .005$), dyspnea (31.4 vs 15.3, $P = .03$), and insomnia (41.2 vs 23.1, $P = .009$).

Table 2. Quality of life in patients with thyroid cancer and hypoparathyroidism vs nonhypoparathyroidism

EORTC QLQ-C30 functioning scales	All (n = 89)	HPT (n = 17)	Non-HPT (n = 72)	*P* (HPT vs non-HPT)
Global health (QL)	65.0 (23.3)	51.0 (29.4)	68.5 (20.4)	.03
Physical functioning (PF)	79.6 (20.5)	66.7 (24.3)	82.7 (18.4)	.007
Role functioning (RF)	79.6 (26.7)	66.7 (30.6)	82.7 (24.9)	.02
Emotional functioning (EF)	75.4 (23.2)	56.9 (30.1)	80.0 (18.8)	.004
Cognitive functioning (CF)	80.8 (23.5)	71.6 (27.5)	83.1 (22.1)	.06
Social functioning (SF)	82.8 (23.5)	69.6 (33.5)	86.0 (19.4)	.04
EORTC QLQ-C30 symptom scales				
Fatigue (FA)	32.0 (28.9)	45.8 (33.1)	28.7 (27.1)	.04
Nausea and vomiting (NV)	6.4 (16.1)	4.9 (9.8)	6.8 (17.3)	.86
Pain (PA)	22.1 (29.6)	41.2 (36.4)	17.6 (26.1)	.005
Dyspnea (DY)	18.4 (24.6)	31.4 (32.2)	15.3 (21.6)	.03
Insomnia (SL)	26.6 (31.5)	41.2 (27.7)	23.1 (31.5)	.009
Appetite loss (AL)	12.9 (25.0)	19.6 (29.0)	11.3 (23.9)	.14
Constipation (CO)	19.2 (27.7)	23.5 (34.9)	18.1 (25.8)	.8
Diarrhea (DI)	13.4 (24.7)	17.7 (31.4)	12.9 (22.9)	.78
Financial difficulties (FI)	17.2 (30.4)	27.5 (39.5)	14.8 (27.6)	.2

Mean represents SD. Mann-Whitney *U* test was used for comparison in quality of life scores between HPT and non-HPT patients.
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HPT, hypoparathyroidism; QLQ-C, Quality of Life Core Questionnaire.

Factors associated with quality of life

Results from the multiple ordinal regression analysis are presented in Table 3. Participants with HPT (compared to no HPT) were statistically significantly less likely to report higher scores (better QOL) for global health (odds ratio [OR], 0.29; 95% CI, 0.10-0.80), physical functioning (OR, 0.22; 95% CI, 0.08-0.58), role functioning (OR, 0.27; 95% CI, 0.10-0.75); emotional functioning (OR, 0.20; 95% CI, 0.07-0.60), and social functioning (OR, 0.30; 95% CI, 0.10-0.87). For symptom scales, HPT patients were more likely to have higher scores (more symptom-related problems) in fatigue (OR, 2.81; 95% CI, 1.06-7.62), pain (OR, 4.47; 95% CI, 1.62-12.67); dyspnea (OR, 3.16; 95% CI, 1.05;9.83), and insomnia (OR, 4.49; 95% CI, 1.59-12.90). Significant associations were also seen for female sex and age in certain domains. No significant associations were seen for Union for International Cancer Control TNM Classification (UICC) stage. Two additional ordinal regression models were performed including TKI treatment (no treatment vs. current treatment) and type of surgery (hemi/partial thyroidectomy vs total thyroidectomy) to adjust for these potential confounders. Both regression analysis showed no pronounced differences in results to the original model (26).

Hypoparathyroidism symptoms

HPT patients reported a significantly higher percentage of tingling or numbness in fingers or toes (65% vs 32%, $P = .03$) and for restlessness or agitation (77% vs 46%, $P = .05$) compared to the non-HPT group. High percentages were reported by both groups regarding pain in the joints (82% vs 54%, $P = .06$), attacks of tiredness (77% vs 51%, $P = .11$), and muscle cramps (59% vs 38%, $P = .18$). An overview about the reported symptoms can be found in Table 4.

Discussion

Our analysis showed that patients with permanent HPT have significant impairments in QOL. HPT patients reported significantly worse scores in global health, physical functioning, role functioning, emotional functioning, social functioning, fatigue, pain, dyspnea, and insomnia.

The study shows that 12% of participants suffered from permanent HPT. These findings are in line with other studies of thyroid cancer patients. A survey among members of self-help organizations for thyroid cancer in 2010 showed that low calcium levels were still reported for 14% of participants 1 year after diagnosis (27). A recent survey among members of a European thyroid cancer self-help organization reported that 19.8% of participants still had low serum calcium levels more than 1 year postdiagnosis (LebenOhneSchilddrüse e.V., data not published).

No significant differences were observed between age, sex, time since diagnosis, education, histology, and TNM among HPT and non-HPT patients. Furthermore, there were small but not significant differences between treatments for the 2 groups. Both groups had slightly different proportions of patients undergoing chemotherapy and treatment with TKIs. These treatments have shown to be associated with side effects (28-30) that might negatively

Table 3. Multiple ordinal regression analysis to evaluate quality of life scores with independent variables

	EORTC QLQ-C30—functioning scales					
Independent variables (reference)	Global Health	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning
Age, y	0.99 (0.96-1.02)	0.96[a] (0.92-0.99)	0.96[a] (0.93-0.99)	1.01 (0.98-1.04)	0.99 (0.96-1.03)	1.00 (0.97-1.04)
Female sex (male)	0.54 (0.23-1.23)	0.40[a] (0.17-0.95)	0.33[a] (0.11-0.85)	0.27[a] (0.11-0.66)	0.77 (0.30-1.92)	0.83 (0.31-2.11)
HPT (no HPT)	0.29[a] (0.10-0.80)	0.22[a] (0.08-0.58)	0.27[a] (0.10-0.75)	0.20[a] (0.07-0.60)	0.38 (0.14-1.04)	0.30[a] (0.10-0.87)
UICC (stage I + II)						
III + IV	1.03 (0.34-3.14)	1.86 (0.59-5.90)	2.03 (0.64-6.78)	0.82 (0.26-2.67)	0.86 (0.27-2.75)	2.47 (0.67-10.09)
Unknown	0.92 (0.24-3.51)	1.98 (0.45-8.69)	2.72 (0.63-13.30)	0.84 (0.19-3.74)	0.46 (0.12-1.79)	1.45 (0.30-8.35)
	EORTC QLQ-C30—symptom scales					
	Fatigue	Pain	Dyspnea	Insomnia	Appetite loss	Constipation
Age, y	1.03 (0.99-1.06]	1.01 (0.97-1.04)	0.99 (0.95-1.03)	1.04[a] (1.01-1.08)	0.99 (0.94-1.03)	1.02 (0.99-1.06)
Female sex (male)	2.85[a] (1.22-6.84)	1.75 (0.69-4.71)	1.06 (0.39-2.97)	3.32[a] (1.21-10.23)	1.92 (0.60-7.51)	3.08[a] (1.06-10.51)
HPT (no HPT)	2.81[a] (1.06-7.62)	4.47[a] (1.62-12.67)	3.16[a] (1.05-9.83)	4.49[a] (1.59-12.90)	1.64 (0.49-5.07)	1.47 (0.43-4.75)
UICC (stage I + II)						
III + IV	0.84 (0.28-2.49)	0.71 (0.20-2.47)	1.29 (0.34-4.94)	0.30 (0.08-1.05)	3.67 (0.84-18.18)	0.38 (0.09-1.49)
Unknown	1.00 (0.24-4.06)	1.28 (0.28-5.59)	9.65 (1.97-53.44)	1.09 (0.21-5.58)	1.40 (0.16-9.82)	0.42 (0.07-2.10)
	Diarrhea	Financial difficulties				
Age, y	0.99 (0.95-1.03)	0.98 (0.94-1.02)				
Female sex (male)	0.43 (0.16-1.22)	0.84 (0.30-2.50)				
HPT (no HPT)	1.22 (0.34-3.96)	2.01 (0.62-6.22)				
UICC (stage I + II)						
III + IV	1.52 (0.36-6.50)	1.04 (0.23-4.52)				
Unknown	1.04 (0.13-6.35)	1.34 (0.16-8.36)				

Functioning scales: odds ratio for scoring higher on respective scale compared to reference group (CI).
Symptom scales: odds ratio for scoring higher on respective scale compared to reference group (CI).
Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; HPT, hypoparathyroidism; QLQ-C, Quality of Life Core Questionnaire; UICC, Union for International Cancer Control TNM Classification.
[a]Statistically significant.

influence QOL. However, because a larger number of participants in the non-HPT group were undergoing treatment compared to those in the HTP group, it is unlikely that differences in QOL between the 2 groups are due to treatment side effects. As seen in the regression analysis, UICC stage had no influence on QOL scores and having HPT was associated with worse scores for various functioning and symptom scales of the QLQ-C30. The reduced QOL may be explained by hypocalcemic symptoms (17, 31), but since few differences in HPT symptoms occurred it is possible that the impairments captured in QOL scores are due to the HPT deficiency itself. Studies have reported that PTH receptors are expressed in a variety of cells, including different organs, the central nervous system, and muscle cells (32-36). One can assume that participants in the HTP group had been taking medication for a considerable time for HPT; therefore, impairments may be explained by the potential short or long-term complications associated with the highly dosed calcium and vitamin D treatment (2, 7, 37).

To date, the majority of the studies assessing QOL in HPT patients have shown a reduced QOL using generic questionnaires in comparison to a healthy population or to matched controls (3, 6, 11, 13-16). The impact of thyroid cancer has seldom been assessed in these studies. One of the largest QOL studies carried out among HPT patients presented 283 HPT patients with a reduced QOL compared to a healthy population. Although 70% of participants had postsurgical HPT, no reasons for surgery were available (6).

Table 4. Typical hypoparathyroid symptoms. Percentage of patients reporting any problem/symptom

Symptom	HPT (n = 17)	No HPT (n = 72)	*P* (HPT vs non-HPT)
Attacks of tiredness	13 (76.5%)	37 (51.4%)	.11
Restlessness or agitation	13 (76.5%)	33 (45.8%)	.05
Pain in the joints	14 (82.4%)	39 (54.2%)	.06
Tingling or numbness in fingers or toes	11 (64.7%)	23 (31.9%)	.03
Tingling or numbness around mouth	3 (17.6%)	8 (11.1%)	.74
Muscle cramps	10 (58.8%)	27 (37.5%)	.18
Rapid heartbeat	10 (58.8%)	28 (38.9%)	.10

Chi-square test was applied for the comparison of symptoms between HPT patients and non-HPT patients.
Abbreviation: hypoparathyroidism.

A study by Sikjaer et al (14) that showed decreased QOL in HPT patients compared to a healthy population stated that surgery for thyroid cancer was performed for 12 out of the 62 (19%) patients, but the potential impact of the thyroid cancer itself was not discussed.

HPT is seldom assessed in studies evaluating the QOL in thyroid cancer patients. The findings of our study show that patients with HPT after thyroid cancer report a worse QOL than patients without HPT after thyroid cancer. A study by Goldfarb and Casillas (20) reported that young adults with HPT after thyroid cancer reported significantly worse scores in the neuromuscular scale and sympathetic scales of the THYCA-QOL, whereas HPT effects on thyroid cancer patients' QOL were not observed in other studies with smaller numbers of HPT patients (38, 39).

The results for typical HPT symptoms are in line with the literature. Two symptoms were statistically significant between HPT and non-HPT patients, but large nonsignificant differences in symptoms between the 2 groups were observed that might foster further investigation with increased power. Some of the most pronounced symptoms in our study were also found in the PARADOX study, including fatigue, muscle pain, or tetany, in 374 participating HPT patients (31). Nevertheless, a high number of patients in the non-HPT group also reported symptoms considered typical for those with HPT. However, it is possible that symptoms can be directly related to thyroid cancer because they are not exclusively linked to HPT, like fatigue, which is often seen in cancer survivors (21, 40).

A limitation of our study is that we do not have information regarding the date of surgery for thyroid cancer and therefore are not able to determine the exact duration of HPT. Nevertheless, as supported by the literature, all patients with thyroid cancer should receive treatment within 3 months after diagnosis of thyroid cancer. Therefore, we can be confident that HPT participants can be considered permanent cases, having lived with HPT for at least 6 months. HPT status was extracted from the medical charts and therefore we cannot exclude that different definitions for "*parathyroid insufficiency*" were applied between the different recruiting centers. However, since all centers are experienced in treating thyroid diseases, the risk of patients being falsely characterized is extremely low. Because this is a secondary analysis of a study that was conducted for another research question (pilot testing of a questionnaire), data for blood tests and medication were unavailable, and the questionnaires in use were preset. Since patients were interviewed in 2015 and 2016 and recombinant PTH was approved by the European Medicines Agency in 2017, we are confident that all patients were treated with calcium and vitamin D analogues at the time of the interview. With no data regarding medication and current calcium levels, we cannot exclude that patients were on stable calcium levels. Nevertheless, the severity of symptoms cannot be directly translated to serum calcium levels (4) and the HPT deficit itself might cause impairments (32-36).

In addition, there was no assessment of comorbidities in the patient population, but the results of the effect of comorbidities on QOL is contradictory (18, 19, 40). Nevertheless, in some of the patients the HPT symptoms might be related to other diseases. Furthermore, most patients showed good performance status as assessed by the Karnofsky Performance Status, indicating no major impairments. Considering the rarity of the disease, a strength of the analysis is the relatively large group of patients with permanent HPT after treatment for thyroid cancer and the well-defined and acceptably sized control group of patients with thyroid cancer, making the impact of HPT alone identifiable. Additionally, a well-validated and widely used disease-specific tool for the measurement of QOL in cancer patients was used. At the time of the study, no well-validated single tool for HPT was available. Third, treatment status for the patients was available, making it possible to minimize potential impairments of QOL due to current treatment in our analysis.

To our knowledge, this is one of the first studies comparing the QOL of patients with HPT after thyroid cancer treatment with patients without HPT after thyroid cancer treatment. Patients with HPT reported significantly worse QOL in 5 out of 6 functioning scales and 4 out of 0 symptom scales of the EORTC QLQ-C30, indicating impairments in QOL. Both groups showed a high prevalence of typical HPT symptoms even more than 9 months after the diagnosis of thyroid cancer. The assessment of HPT in studies measuring the QOL in thyroid cancer patients should be considered

because our analysis has shown that HPT might severely influence the QOL of thyroid cancer survivors.

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Data Availability: The data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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8.3 Büttner et al. (2022) - What are predictors of impaired quality of life in patients with hypoparathyroidism?

Zusammenfassung

Einleitung: Hypoparathyreoidismus (hypoPT) ist eine seltene endokrine Erkrankung, bei der bisher wenig über mögliche Faktoren bekannt ist, die die Lebensqualität der Patienten beeinflussen.

Methoden: Patienten mit einer mindestens sechs Monate bestehenden hypoPT Diagnose wurde über Selbsthilfe-Organisationen oder ihre behandelnden Ärzte zur Teilnahme an einer Online-Umfrage eingeladen. Dort machten sich auch Angaben zu ihrer Lebensqualität. Sofern die Funktionsskalen des EORTC QLQ-C30 einen bestimmten Grenzwert überschritten, wurden klinisch relevante Einschränkungen in der entsprechenden Skala für den Patienten dokumentiert. Symptome wurden mittels des HPQ-28 gemessen. Multivariate logistische Regressionen zur Bestimmung von Bereichen die mit Lebensqualitätseinschränkungen assoziiert sind, wurden durchgeführt.

Ergebnisse: Auswertenbare Daten von 264 hypoPT Patienten waren verfügbar für die Analyse. Klinisch relevante Einschränkungen der Lebensqualität wurden bei 40.4% (Rollenfunktion), 40.6% (soziale Funktion), 60.8% (physische Funktion), 65.5% (kognitive Funktion) und 76.0% (emotionale Funktion) der Patienten festgestellt. Höhere Odds für klinisch relevante Einschränkungen wurde für höhere Symptombelastung und Arbeitsunfähigkeit (für physische Funktion, Rollenfunktion und soziale Funktion) festgestellt. Wenn eine Schilddrüsenkrebs-Operation die Ursache für den hypoPT war, war dies mit niedrigeren Odds für klinisch relevante Einschränkungen in der Skala physische Funktion assoziiert.

Fazit: HypoPT ist eine Erkrankung die sich negativ auf die Lebensqualität auswirken kann. Um die Lebensqualität von hypoPT Patienten zu steigern ist ein optimales Symptommanagement notwendig, aber auch sozioökonomische Faktoren sollten in der Nachsorge berücksichtigt werden.

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ORIGINAL ARTICLE

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What are predictors of impaired quality of life in patients with hypoparathyroidism?

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Abstract

Context: Hypoparathyroidism (hypoPT) is a rare endocrine disorder. Little is known about what factors are associated with potential quality of life (QOL) impairments.

Design: HypoPT patients at a minimum of 6 months' post diagnosis were invited to participate in an online survey through their treating physician or through self-help organisations

Methods: Impairments of clinical importance in QOL were considered present if the score of the respective functioning scale of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 exceeded a pre-defined threshold. Symptom burden was assessed using the HPQ-28. Multivariate logistic regression was used to identify factors associated with impairments in QOL.

Results: Data were available for 264 hypoPT patients. Impairments of clinical importance in QOL were reported for 40.4% in role functioning (RF), 40.6% in social functioning (SF), 60.8% in physical functioning (PF), 65.5% in cognitive functioning (CF) and 76.0% in emotional functioning (EF). Higher odds for reporting impaired QOL were seen for higher symptom burden (for almost all domains) and for being unable to work (for PF, RF and SF). Surgery for thyroid cancer being the cause of hypoPT was associated with lower odds in PF for patients and in PF and CF for patients with surgery for other thyroid-related diseases being the hypoPT cause.

Conclusions: HypoPT needs to be recognised as a disease which might be associated with impaired QOL and affect daily living. Symptom management is crucial for improving QOL in hypoPT patients but socioeconomic factors like work-ability need to be considered when treating hypoPT patients.

KEYWORDS

EORTC QLQ-C30, hypoparathyroidism, impairments, parathyroid, quality of life, survey, well-being

1 | INTRODUCTION

Chronic Hypoparathyroidism is an endocrine disorder defined hypocalcaemia with inappropriately normal or low parathyroid hormone[1,2] for more than 6 months but different definitions and times frames are also used in the literature.[3] The prevalence varies in countries with 9.4 per 100,000 in Norway,[4] 24 per 100,000 in Denmark[5,6] and 37 per 100,000 in the United States.[7] The current treatment options consist of calcium and vitamin D supplementation as the conventional treatment, and synthetic PTH analogue (PTH 1–34) and human recombinant parathormone (PTH 1–84) as new treatment options for patients whose hypocalcemia cannot be treated with the standard treatment.[1] Patients receiving standard treatment have been shown to report impairments in quality of life (QOL) compared to matched controls or norm populations.[8,9] Studies using PTH 1–34 or PTH 1–84 have been shown to improve QOL[10–12] and to maintain calcium levels in the normal target range.[9] Therapies and blood level parameters might play a role in influencing QOL in hypoPT patients, but the role of blood levels results in particular is conflicting in the literature.[4,9,11] The severity of symptoms and therefore their influence on QOL cannot be directly translated to serum calcium levels,[1] since calcium levels may vary throughout the day and therefore single measures might not explain effects on QOL.[13] Factors like symptoms, disease duration, aetiology of hypoPT, or sociodemographic factors may play an important role in the QOL of hypoPT patients.

Therefore, the aim of this study was to assess the share of hypoPT patients who report impairments in QOL of clinical importance and to identify factors which might be associated with impaired QOL.

2 | MATERIALS AND METHODS

2.1 | Design

Supported by the German Society of Endocrinology, Hormones, and Metabolism and the German Society of Nuclear Medicine, physicians were informed about the study and invited to provide information to their patients. Additionally, 294 physicians were contacted by mail and were asked for their support of the study with 22 (7.5%) actively consenting to support the study. The contact information of the physicians was obtained using the Kassenärztliche Budesvereinigung database. They then informed their patients about the study. Additionally, study information was distributed through the patient organisation Netzwerk Hypopara. Patients completed on online survey between 10/2020 and 10/2021. Next to the online questionnaire, a paper-based version of the questionnaire was available and was provided upon request.

Patients were eligible if they had been treated for hypoparathyroidism diagnosed by their physician. As per local regulations, no ethics committee approval was needed (confirmed by the Ethics-Committee of the Landesärztekammer Rhineland-Palatinate).

2.2 | Assessments

All data were provided by the patient through the online survey. QOL was assessed using the functioning scales [physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF)] and the global QOL scale of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30).[14] Response formats are on a four-point-Likert scale ('not at all', 'a little', 'quite a bit' and 'a lot'). The items are summarised and transformed into scores ranging from 0 to 100, with high values indicating lower impairments in the functioning and the QL scales.[15] Symptom Burden was assessed using the Hypoparathyroid Patient Questionnaire HPQ-28.[16] In the HPQ-28, 20 symptom items using a four point-Likert Scale (0 = 'not at all', 1 = 'slightly', 2 = 'moderately', 3 = 'severely/strongly') measure symptom burden and eight items for the assessment of depression and anxiety and vitality. The items cover symptoms related to *pain and cramps*, *gastrointestinal symptoms*, *neurovegetative symptoms*, *numbness or tingling*, *memory problems*, *heart palpitations*, *depression and anxiety* using a 4-week time frame. For categorising symptom burden, the mean value of all items (scores ranging from 0 to 3 per question) was calculated. Participants were categorised into *low symptom burden* (mean score 0 to <0.5), *medium symptom burden* (mean score ≥0.5 to <1.5), and *high symptom burden* (mean score ≥1.5). Education was defined by the highest educational certificate obtained resulting into the following categories: *below 10 years of education*, *10 years of education*, *and above 10 years of education*. Occupational status was assessed by the current employment situation. Four categories emerged from the question: *Employed/self-employed*, *retirement annuity (regular retirement)*, *unable to work*, and *others*. The *unable to work* category comprises patients who are early retired (before the age of 65), receive disability pension, reduced earning capacity pension, or are on long-term sick leave (more than 6 months). In the *other* category participants were included if the total numbers were too small to form a group (e.g., students, housewives). Time since diagnosis was assessed using the following categories: *0.5–1*, *1–2*, *2–5*, *5–10 years*, and *more than 10 years*.

2.3 | Statistical analysis

Scores for the functioning scales of the EORTC QLQ-C30 were calculated according to the scoring manual of the EORTC.[15] A value below the thresholds (PF: 83 points, RF: 58 points, SF: 58 points, EF: 71 points, and CF: 75 points) by Giesinger et al.[17] was considered to be an impairment of clinical importance in the respective scale. Univariate comparisons of QOL scores (non-surgical vs. surgical) were performed using Mann–Whitney-*U* tests.

Multivariate logistic regression with having impairments of clinical importance (no/yes) as the outcome and sociodemographic, clinical, and symptom burden as independent variables was performed for the five functioning scales of the EORTC QLQ-C30. All

TABLE 1 Patient characteristics (n = 264) using mean (SD) or n (%)

Characteristic	
Age (mean [SD])	54.5 (13.3)
Sex (n [%])	
Male	36 (13.6%)
Female	225 (85.2)
Missing	3 (1.1)
Education (n [%])	
Below 10 years	36 (13.6)
10 years	102 (38.6)
More than 10 years	125 (47.3)
Missing	1 (0.4)
Living situation (n [%])	
Alone	61 (23.1)
With someone	203 (76.9)
Occupation (n [%])	
Employed/self-employed	145 (54.9)
Regular retirement	57 (21.6)
Unable to work	45 (17.0)
Other	17 (6.4)
Member of self-help organization (n [%])	
No	167 (63.3)
Yes	97 (36.7)
Time since diagnosis (n [%])	
6 months–1 year	6 (2.3)
1–2 years	22 (8.3)
2–5 years	47 (17.8)
5–10 years	43 (16.3)
More than 10 years	145 (54.9)
Missing	1 (0.4)
Cause of HPT (n [%])	
Nonsurgical	21 (8.0)
Surgical	243 (92.0)
Surgery for thyroid cancer	100 (41.2)
Surgery for other thyroid related diseases	143 (58.8)
Symptom burden (n [%])	
None to low	59 (22.3)
Medium	75 (28.4)
High	130 (49.2)
Medication (n [%])	
Calcium	153 (58.0)
Calcitriol	152 (57.6)
Alphacalcidol	23 (8.7)
Colecalciferol	66 (25.0)
PTH	28 (10.6)
Magnesium	49 (18.6)
Dihydrotachysterol	31 (11.7)
Missing	13 (4.9)

statistical analyses were performed using R (R version 4.0.4, R Foundation for statistical computing).

3 | RESULTS

3.1 | Sample and patient characteristics

In total, 264 patients with hypoparathyroidism participated in the study. Four (2.3%) participants were excluded since their diagnosis was less than 6 months past and therefore it could not be ruled out that their hypoPT was only transient. The mean age of the study population was 54.5 (SD:13.3) years with 85.2% (225) being female and 92.0% (243) naming surgery the cause for their hypoPT. All patient characteristics can be found in Table 1.

3.2 | Quality of life

QOL scores for the total sample and for patients with non-surgical and surgical causes of hypoPT are presented in Table 2. No differences were seen when comparing the QOL scores of patients with a non-surgical and surgical cause using univariate analysis.

For role functioning and social functioning 40.4% and 40.6% of the patients reported impairments of clinical importance. For the three other functioning scales, the percentage of patients with impairments of clinical importance was 76.0% regarding emotional functioning, 60.8% in physical functioning, and 65.5% in cognitive functioning.

3.3 | Factors associated with impairments in QOL in patients with hypoparathyroidism

Symptom burden was associated with all functioning scales (Table 3). Compared to patients with a medium symptom burden, patients with low symptom burden had lower odds for impairments of clinical importance {PF (OR: 0.1; 95% CI [0; 0.3]), EF (OR: 0.2; 95% CI [0.1; 0.4]), SF (OR: 0.04; 95% CI [0.002; 0.2]), and CF (OR: 0.2; 95% CI [0.1; 0.6])} and patients with high burden reported higher odds

TABLE 2 Functioning in patients with hypoparathyroidism (HPT), stratified by cause of HPT (surgery vs. other causes)

		All (*n* = 264)	Non-surgical (*n* = 21)	Surgical (*n* = 243)	*p*-value non-surgical versus surgical)
Physical functioning (PF)	Mean (SD)	74.0 (21.5)	74.3 (17.2)	74.0 (21.9)	.75
	Median (Q1;Q3)	80 (60; 93.3)	73.3 (60; 80)	80 (60; 93.3)	
Role functioning (RF)	Mean (SD)	63.6 (32.5)	65.9 (35.9)	63.4 (32.3)	.62
	Median (Q1;Q3)	66.7 (33.3; 100)	66.7 (33.3; 100)	66.7 (33.3; 100)	
Social functioning (SF)	Mean (SD)	61.7 (33.4)	69.0 (33.5)	61.1 (33.4)	.28
	Median (Q1;Q3)	66.7 (33.3; 100)	83.3 (50; 100)	66.7 (33.3; 100)	
Emotional functioning (EF)	Mean (SD)	46.9 (30.1)	54.5 (30.5)	46.2 (30.0)	.22
	Median (Q1;Q3)	50 (25; 66.7)	58.3 (41.7; 75)	50 (22.2; 66.7)	
Cognitive functioning (CF)	Mean (SD)	56.9 (31.6)	63.5 (27.7)	56.3 (32.0)	.38
	Median (Q1;Q3)	66.7 (33.3; 83.3)	66.7 (50; 83.3)	66.7 (33.3; 83.3)	
Global Quality of Life (QL)	Mean (SD)	44.4 (21.3)	44.0 (21.8)	44.4 (21.3)	.84
	Median (Q1;Q3)	50 (33.3; 58,3)	50 (33.3; 58,3)	50 (33.3; 58,3)	

Note: Univariate comparison using Mann–Whitney-*U* tests.

{PF (OR: 4.3; 95% CI [2.1; 9.2]), RF (OR: 7.5; 95% CI [3.6; 16.4]), EF (OR: 7.9; 95% CI [3.0; 24.2]), SF (OR: 4.9; 95% CI [2.4; 8.8]), and CF (OR: 12.0; 95% CI [5.3; 29.8])} for impairments of clinical importance.

Patients who were unable to work (compared to patients being employed/self-employed) had higher chances of reporting impairments of clinical importance in PF (OR: 6.3; 95% CI [2.1; 21.7]), RF (OR: 5.6; 95% CI [2.2; 15.2], and SF (OR: 2.6; 95% CI [1.1; 6.6]). Surgery being the cause of hypoPT (compared to non-surgical patients) was associated with lower odds in PF (OR: 0.1; 95% CI [0; 0.5]) for patients with surgery for thyroid cancer and in PF (OR: 0.1; 95% CI [0; 0.4]) and CF (OR: 0.3; 95% CI [0.1; 0.9]) for patients with surgery for other thyroid-related diseases (e.g., goitre). Compared to the lowest education group (below 10 years of education), education of 10 years (OR: 0.2; 95% CI [0.1; 0.6]) and above 10 years (OR: 0.3; 95% CI [0.1; 0.9]) was associated with lower odds in PF. Age, living with someone, and time since diagnosis were not associated with impairments of clinical importance in the functioning scales. PTH replacement therapy did not alter the results of the regression analysis and did not show any significant associations (data not shown).

4 | DISCUSSION

Our study shows that a moderate to high share of patients report impairments of clinical importance across several QOL domains. Patients with a medium and high symptom burden had higher chances of reporting impairments in QOL. Being unable to work was also associated with higher odds of reporting impairments in PF, RF and SF of the EORTC QLQ-C30.

With 40.4% (for RF) and up to 76.0% (for EF), our study had a moderate to high share of hypoPT patients with impairments of clinical importance. These potential negative effects of hypoPT on QOL are in line with findings from other studies assessing the QOL in hypoPT patients.[8] Compared to various cancer populations, an equal or higher share of patients reported impairments of clinical importance in our study.[18,19] This is in line with findings from Astor et al.[4] who reported, using the SF-36, that Norwegian hypoPT patients had significantly lower scores compared to patients with Addison's disease or congenital adrenal hyperplasia. Oerlemans et al.[20] found that for thyroid cancer survivors large differences regarding self-reported cognitive functioning (using the EORTC QLQ-C30) compared to a norm population exist. Since it is estimated that up to 17%[21] of all patients with total thyroidectomy develop chronic hypoPT, the question arises if these impairments in cognitive functioning might not also be applicable to hypoPT among thyroid cancer survivors since cognitive functioning was the second highest domain with reported impairments in our study and the so-called brain fog being one of the typical hypoPT symptoms.[1] In general, the question arises if impairments in QOL of thyroid cancer patients and survivors might not be influenced be the occurrence of hypoPT in this population.[22] On the other hand, one can also discuss whether the cause of hypoPT (e.g., surgery for thyroid cancer) does have an effect on QOL itself. The aetiology hypoPT as an impact on QOL is controversially discussed in the literature. While some studies report worse QOL for surgical hypoPT patients compared to non-surgical,[4,9] this could not be confirmed in our study. In our study, having thyroid cancer as cause for surgery was even associated with lower odds in PF (OR: 0.1; 95% CI [0; 0.5]) of reporting impairments of clinical importance compared to non-surgical patients. One possible

TABLE 3 Variables associated with clinically impaired functioning in patients with hypoparathyroidism

	Physical functioning (PF)	Role functioning (RF)	Emotional functioning (EF)	Social functioning (SF)	Cognitive functioning (CF)
Age (continuous)	1.0 [1.0; 1.0]	1.0 [1.0; 1.1]	1.0 [0.9; 1.0]	1.0 [1.0; 1.0]	1.0 [0.9; 1.0]
Sex					
Male (ref.)	1	1	1	1	1
Female	1.5 [0.5; 4.3]	1.0 [0.4; 3.1]	1.0 [0.4; 2.6]	1.2 [0.4; 3.8]	0.8 [0.3; 2.2]
Education					
Below 10 years (ref.)	1	1	1	1	1
10 years	0.2 [0.1; 0.6]*	0.5 [0.2; 1.4]	0.8 [0.2; 2.6]	0.7 [0.3; 1.8]	1.3 [0.5; 3.6]
Mmore than 10 years	0.3 [0.1; 0.9]*	0.5 [0.2; 1.4]	0.9 [0.3; 2.7]	0.8 [0.3; 2.1]	1.6 [0.6; 4.5]
Living with someone					
No (ref.)	1	1	1	1	1
Yes	0.8 [0.4; 1.8]	0.5 [0.2; 1.1]	0.7 [0.3; 1.7]	0.7 [0.4; 1.5]	1.0 [0.4; 2.1]
Occupation					
Employed/self-employed (ref.)	1	1	1	1	1
Regular retirement	1.4 [0.4; 4.6]	0.6 [0.2; 1.8]	0.5 [0.1; 1.7]	0.7 [0.2; 2.1]	1.1 [0.3; 3.7]
Unable to work	6.3 [2.1; 21.7]*	5.6 [2.2; 15.2]*	0.9 [0.3; 2.9]	2.6 [1.1; 6.6]*	2.6 [0.9; 7.9]
Other	0.8 [0.2; 3.4]	1.1 [0.3; 3.9]	0.3 [0.1; 1.7]	1.9 [0.5; 7.8]	0.6 [0.1; 2.6]
Cause of HPT					
Non-surgical (ref.)	1	1	1	1	1
Surgical—thyroid cancer	0.1 [0; 0.5]*	0.3 [0.1; 1.1]	2.4 [0.6; 9.5]	0.7 [0.2; 2.6]	0.4 [0.1; 1.7]
Surgical—other reason	0.1 [0; 0.4]*	0.5 [0.1; 1.6]	1.1 [0.3; 4.0]	0.8 [0.2; 3.1]	0.3 [0.1; 0.9]*
Time since diagnosis					
6 months–2 years (ref.)	1	1	1	1	1
2–5 years	1.8 [0.5; 6.1]	1.4 [0.5; 4.5]	2.1 [0.5; 9.7]	1.4 [0.5; 4.3]	1.8 [0.5; 7.2]
More than 5 years	0.9 [0.3; 2.6]	0.6 [0.2; 1.7]	1.8 [0.5; 6.0]	1.0 [0.4; 2.6]	1.3 [0.4; 4.0]
Symptom burden					
None to low	0.1 [0; 0.3]*	0.3 [0.1; 1.0]	0.2 [0.1; 0.4]*	0.04 [0; 0.2]*	0.2 [0.1; 0.6]*
Medium (ref.)	1	1	1	1	1
High	4.3 [2.1; 9.2]*	7.5 [3.6; 16.4]*	7.9 [3.0; 24.2]*	4.9 [2.4; 8.8]*	12.0 [5.3; 29.8]*

Note: OR [95% CI]; (ref.), reference category. Multivariate logistic regression.
*$p < .05$.

explanation that surgical patients did not report lower QOL scores might be that surgical patients are monitored more closely in aftercare and therefore physicians are able to address QOL issues in a better way. Also, our non-surgical group is quite small ($n = 21$), which might make it difficult to find differences. Additionally, our multivariate analysis showed that patients with medium or high symptom burden had higher chances of reporting impairments in QOL across all functioning domains of the EORTC QLQ-C30. These results are not surprising and in line with findings from the literature.[23,24] Even though all patients in our study were currently being treated, around 75% of the patients in our study reported a medium or high symptom burden assessed by the HPQ-28. This finding supports the recommendation of the guideline published by the European Society of Endocrinology in 2015 which describes the general goals of management of hypoPT as being that '[…] treatment targeted to maintain serum calcium level (albumin adjusted total calcium or ionised calcium) in the lower part or slightly below the lower limit of the reference range (target range) with patients being free of symptoms or signs of hypocalcaemia.' They also 'recommend that treatment be personalised and focused on the overall well-being and QOL of the

patient when implementing different therapeutic efforts, aiming to achieve the therapeutic goals'.[1] Findings from our study did not show any association between time since diagnosis and QOL. These findings are in line with results from other studies indicating that impairments in QOL do not disappear over time, potentially affecting patients for the rest of their life.[25,26] Being unable to work (compared to employed/self-employed) was associated with higher odds of reporting impairments in PF (OR: 6.3; 95% CI [2.1; 21.7]), RF (OR: 5.6; 95% CI [2.2; 15.2], and SF (OR: 2.6; 95% CI [1.1; 6.6]). In our study, 17.0% of the patients were not able to work anymore. A study by Hadker et al.[24] reported that 14% of the patients reported 'disabled' as their employment status over the course of their diagnosed lifetime, while Siggelkow et al.[23] reported the percentage of hypoPT patients who are working decreased from 58% before diagnosis to 34% at the time of the survey. The negative effect of being unable to work has been observed in other diseases such as breast cancer[27] or coronary heart disease.[28] One possible explanation for this association might be the loss of income due to loss of work. Studies in cancer patients have shown that financial difficulties are associated with impairments in QOL.[29,30] For example in Germany, the average full disability pension which applies if you are not able to work more than 3 h a day, was €850 in 2019.[31] Such income declines, especially in age groups who were not able to accumulate savings or who had investments might cause financial problems and therefore impairments in QOL.[30] Another possible explanation might be that being able to work may be seen as a return to 'normality'.[28] Third, free text analysis in our study has shown that patients felt that employers and public authorities have no information regarding hypoPT or do not acknowledge the severity of the disease. This has been expressed by authorities and physicians not accepting hypoPT in certain cases as a severe disability, resulting in disability pension and disability pass. This empathy gap related to work might be an explanation for the association of being unable to work and QOL. The aforesaid empathy gap is not only restricted to employers and authorities. Free textes of our survey and other studies[24,32] report that hypoPT patients feel that physicians do not understand hypoPT and its burden the way the patients feel it. In Hadker et al.[24] almost 80% of the hypoPT patients 'strongly agreed' that most physicians do not understand hypoPT. Cho et al.[32] showed that surgeons consistently underestimated the impact of postoperative hypoPTH. This empathy gap and missing knowledge regarding the disease, independently where it occurs, might negatively impact hypoPT patients QOL. 28 patients in the study were treated with PTH replacement. PTH replacement did not have any significant effect on QOL (data not shown) which is in contrast to findings from the literature.[10–12] We do not have any information on how long patients in our study are already receiving PTH replacement. So the duration of the PTH replacement therapy might be too short to provide enough positive effects. Despite all these identified factors, the lack of PTH itself might also have a negative impact on hypoPT patients QOL. PTH receptors have been found in several brain regions, the central nervous system, and in muscle cells. The lack of PTH here may also be a reason for impairments in QOL in hypoPT patients.[33,34]

Our study has several limitations. First, all data provided in this study was obtained personally from the patient and we had no possibility to validate the data by comparing it to patient records. Since we used validated questionnaires and patients were informed by their treating physician or via their self-help organisations, we are confident that all patients included have been diagnosed with hypoPT and their QOL is assessed in a coherent way. Second, this study has a cross-sectional design, making it impossible to detect any longitudinal effects. Third, less than 50% of the patients were able to provide laboratory parameters and comorbidities were not assessed, making it impossible to include these in the analysis. Studies have shown that QOL does not correlate directly with laboratory results[11,21,25,26] and the influence of comorbidities is discussed controversially.[9,21] Our study was a voluntarily online survey which might lead to an inclusion of patients with more severe problems since they are severely affected, but since patients were also recruited through their treating physician we could ensure that the sample was drawn from a representative population. Last, one limitation might be the EORTC QLQ-C30 is a questionnaire developed for cancer patients, but it is also used in various non-cancer populations[35] and shows good correlations in the functioning scales of generic QOL questionnaires in non-cancer populations.[36] Using the QLQ-C30 gives the opportunity to perform comparisons with other thyroid cancer patients (e.g., without hypoPT). Having no control group might be considered as a limitation but not being relevant for identifying factors which influence QOL in hypoPT patients. Additionally, QOL might also be influenced by the COVID 19 pandemic during which the study was performed but this was seldom stated in any of the free text fields. Strengths of our study are the large sample size and the heterogeneity of our study population. Patients were not recruited via one centre or institution but throughout a variety of treating physicians and institutions, therefore resulting in a sample which may be more representative. With a broad set of sociodemographic and clinical variables as well with a disease-specific questionnaire, the HPQ-28,[16] for the assessment of symptoms we were able to identify factors which might impact QOL.

5 | CONCLUSION

High shares of patients with hypoPT report problems of clinical importance in QOL. The occurrence of hypoPT related symptoms is strongly associated with QOL, indicating the need to optimise treatment to reduce of symptoms and not solely rely on laboratory parameters. Additionally, the recognition of hypoPT as a disease which might severely influence daily living and especially the work environment as well as the adoption of supportive opportunities for coping with the disease are of major importance for reducing QOL impairments.

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CONFLICT OF INTERESTS

Matthias Büttner reports speaker fees from Lilly and Takeda outside the submitted work. Dieter Krogh has nothing to disclose. Heide

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ETHICAL APPROVAL

According to the design of the study, no Ethics Committee approval was needed (confirmed by the Ethics-Committee of the Landesärztekammer Rhineland-Palatinate).

AUTHOR CONTRIBUTIONS

All authors participated in critically revising the manuscript and all authors approved the final version of the manuscript for submission. All authors contributed to the conception of the study with Matthias Büttner as principal investigator. Matthias Büttner contributed to the analysis and interpretation of the data and draughted the manuscript. Matthias Büttner will use this paper as part of his PhD thesis. Special thanks go to the Netzwerk Hypopara, the German Society of Endocrinology, Hormones and Metabolism and the German Society of Nuclear Medicine for their support.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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9. Short summary of the results of the three publications

Paper 1 (172) and Paper 2 (171) show that post-surgical hypoPT is associated with worse QoL in hypoPT patients. While Paper 3 (173) provides information showing that in patients with hypoPT, a past diagnosis of TC is not associated with QoL or symptom burden.

9.1 Büttner et al. (2020) - Quality of life of patients more than 1 year after surgery for thyroid cancer

Of the 134 patients which were eligible only 75 (56%) participated in the study. There were no statistically significant differences between participants and non-participants regarding current age, time since surgery, gender, histology, UICC stage, type of surgery, and transplanted or removed parathyroid glands. A potential diagnosis of hypoPT defined as prolonged/ permanent calcium and/or vitamin D intake after thyroid cancer was present in 36 (48%) of the patients. In univariate analyses, patients with calcium and/or vitamin D intake had worse QoL in global health (mean score 68.5 vs. 76.7; p = 0.041), physical functioning (mean score 89.3 vs. 95.7; p = 0.015), role functioning (mean score 77.3 vs. 89.3; p = 0.032), and joint pain (mean score 29.6 vs. 11.1; p = 0.009) compared to patients without calcium and/or vitamin D intake. In multivariate logistic regression, current calcium or vitamin D intake (vs. no intake) had a significant effect on the odds of having a worse QoL compared with the general population in role functioning (OR 4.63; 95% CI [1.28–19.77]) and emotional functioning (OR 3.87; 95% CI [1.11–15.42]).

9.2 Büttner et al. (2020) - Quality of life in patients with hypoparathyroidism after treatment for thyroid cancer

In total 89 TC patients fulfilled the inclusion criteria for the analysis with 17 (19.1%) patients being additionally diagnosed with post-surgical hypoPT. There were no statistically significant differences between the hypoPT group and the no-hypoPT group regarding sociodemographic or clinical characteristics. Compared to patients without hypoPT patients in the hypoPT group scored worse in global health (51.0 vs. 68.5, p=0.03), physical functioning (66.7 vs. 82.7, p=0.007), role functioning (66.7 vs. 82.7, p=0.002), emotional functioning (56.9 vs. 80.0, p=0.004) and social functioning (69.6 vs. 86.0, p=0.004), while cognitive functioning (71.6 vs. 83.1, p=0.06) was not significantly decreased (univariate analysis). In multivariate ordinal regression patients in the hypoPT group had lower odds of reporting higher scores (better QOL) compared to patients without hypoPT in global health (OR: 0.29; 95%CI [0.10;0.80]), physical functioning (OR: 0.22; 95%CI [0.08;0.58]), role functioning (OR: 0.27; 95%CI [0.10;0.75]); emotional functioning (OR: 0.20; 95%CI [0.07;0.60]), and social functioning (OR: 0.30;95%CI [0.10;0.87]). For symptom-scales, hypoPT patients were more likely to have higher scores (more symptom-related problems) in fatigue (OR: 2.81; 95%CI [1.06;7.62], pain

(OR: 4.47; 95%CI [1.62;12.67]; dyspnoea (OR: 3.16; 95%CI [1.05;9.83]), and insomnia (OR: 4.49; 95%CI [1.59;12.90]).

9.3 Büttner et al. (2022) - What are predictors of impaired quality of life in patients with hypoparathyroidism?

In the online survey 264 patients with hypoPT participated of whom 100 (41.2%) had surgery for TC as cause for their hypoPT. Compared to non-surgical hypoPT patients with a history of TC had lower odds of reporting impairments in QoL of clinical importance physical functioning (OR: 0.1; 95%CI [0;0.5]) while for all other scales of the EORTC QLQ-F17 no statistically significant associations were observed. Main predictor for impairments of clinical importance in QoL was symptom burden assessed by the HPQ-28.

10. Discussion of the three publications

The studies show that patients with hypoPT, as a surgical complication of TC treatment, report worse QoL compared to TC patients without hypoPT. There are various reasons that might explain these findings. Symptoms of hypocalcemia (e.g. tingling, cramps, brain fog) might have a negative impact on QoL (112, 174). As seen in study 3, higher symptom burden is associated with higher impairments in QoL in hypoPT patients (173).The occurrence of hypoPT symptoms with respect to blood levels is controversially discussed in the literature (117, 175-178). One other explanation might be the role of the missing PTH itself. Studies have shown that PTH receptors exist in the central nervous system, muscle cells, and several brain regions (179-183). Thirdly, hypoPT and its long-term treatment might cause additional comorbidities like renal stones, calcifications, cardiovascular disease, or cataracts (83, 91), which then might have an impact on QoL. As seen in study 3, the association of TC and QoL in hypoPT patients could not be confirmed indicating an independent influence of hypoPT on QoL. The association between TC and QoL has seldom been assessed in the literature (166, 168, 170) and if so only by generic questionnaires that might miss specific symptoms (46, 47).

All three studies have several limitations. As all studies were of cross-sectional design, the measurement of QoL can only be seen as a snapshot and the study design itself does not allow to draw causal conclusions. Secondly, none of the three studies collected information on co-morbidities, but the effects of co-morbidities on QoL are controversially discussed in the literature (36, 184, 185). And thirdly, the studies did not include extensive blood level parameters, so their effect on QoL could not be determined; however, as described above, the effect of blood levels in hypoPT is discussed controversially (117, 175-178). Lacking information on co-morbidities and extensive blood levels made it impossible to adjust for these potential confounders but their potential influence is not clear throughout the literature.

Strengths of the three studies are the use of a validated QoL questionnaire and the use of norm population data. Study 3 represents the largest hypoPT sample in Germany and one of the largest samples worldwide. Study 1 and study 2 belong to the largest studies in TC patients where hypoPT was included in the analysis of QoL.

11. Discussion

As seen in in the published papers it seems that post-surgical hypoPT after TC negatively affects QoL in TC patients. But several questions arise:

1. How is QoL generally addressed in clinical practice of TC and is the impact of post-surgical hypoPT recognized and addressed for?

2. How are QoL and hypoPT addressed in guidelines?

3. How follow-up of TC patients is organized with special focus on QoL and hypoPT?

4. Are electronic patient reported outcomes (ePROs) suitable for the follow-up of TC patients?

11.1 Guidelines

Various national (186, 187) and international (144-146, 188-201) guidelines exist with only very few who do not address the topic of QoL or hypoPT (189, 190, 196). Two guidelines state in their preamble that the or one the aims of the guideline is to improve QoL of TC patients (188, 199). QoL is often mentioned regarding certain types of TC (188, 191, 192, 195, 197-200) or treatments (146, 186, 191, 192, 195, 199). The assessment of QoL during follow-up is only addressed in few guidelines (146, 191, 195, 197, 199, 201). Guidelines dealing only with anaplastic cancer have a strong focus on QoL (146, 186, 188, 194). For example the American Thyroid Association (ATA) states in their guideline for the management of anaplastic TC (188) that “clinical management must be guided by patient preferences with respect to quality of life, in which there is full disclosure of the diagnosis, realistic prognosis, and treatment options available for either prolonging life”. In the ATA guideline for medullary TC the focus on QoL becomes present when metastasis occur. But this is already connected to the potential side effects of local and systemic treatments (200). The impact of systemic treatments on QoL is addressed in various guidelines (146, 191, 199, 200). The recommendations here address that physicians should take QoL when planning systemic treatment. Another aspect where QoL in guidelines is discussed when it comes to tracheostomy in TC (146, 186, 192, 194). In order to reduce the risk of hypothyroidism and the related impairments in QoL guidelines recommend the use of rhTSH compared to thyroid withdrawal (194, 199). A third treatment related area were QoL is addressed in guidelines is related to the question if microcarcinomas should be treated with surgery or active surveillance (192, 195). Treatment related areas like surgery

itself or radioiodine treatment a seldom addressed with respect to QoL even though it is known that these treatments might influence QoL (36, 202). Before treatment is initiated some guidelines (146, 191, 197, 199) but not all recommend that patients should be informed about the potential negative effects that the treatment can have on QoL. When it comes to follow-up or survivorship only few guidelines give recommendations regarding QoL (146, 191, 194, 197, 199). Perros et al. (199) address the topic by stating that survivors of TC still report impairments in QoL and this needs to be taken care of during follow-up care. Fugazzola et al. (191) advocate that at every follow-up a thoughtful clinical assessment should be performed which takes aspects of quality of life into consideration. In the ATA guideline from 2015 (146) it is still stated that more studies regarding QoL in survivors are needed. Eventhough, quite a few studies have emerged there are still studies lacking which address certain aspects of QoL in survivors. Additionally, in this guideline it is demanded that TC specific instruments for the measurement of QoL need be developed and implemented. At least few TC specific questionnaires are now available (see Section 1) but no guideline gives any recommendation a specific instrument/tool. In general, it can be seen that recommendations addressing quality of life are often only based on expert consensus with little or no level of evidence. This is especially true for follow-up and survivorship. At the time of finalization of this thesis the new German S3-Guideline for thyroid cancer was not publicly available and could therefore not be included in this discussion.

Since the risk of hypoPT after surgery for TC (see Section 3) and the impairments in QoL due to hypoPT (see Section 4) are not neglectable, the question arises how do guidelines for TC address this topic. There are guidelines which don't address the topic at all (188, 190, 192, 196) and one guideline by Perros et al. (199) which addresses it in a very extensive way with its own chapters for hypoPT. The rest of the guidelines do address the topic restricted to certain areas. Some guidelines recommend that patients and caregivers should be informed before surgery about the risk of hypoPT and its consequences (146, 193, 195). When it comes to surgery it is recommended to avoid prophylactic or elective neck dissection due to the risk of hypoPT (144-146, 186, 198, 199). Two guidelines provide information how surgery should be performed in order to minimize (e.g. autotransplantation of parathyroid glands) the risk of hypoPT (146, 199). Recommendations regarding preservation of parathyroid function is crucial since avoiding hypoPT is cheaper that treating hypoPT (203). In order to detect post-surgical hypoPT some guidelines recommend that PTH and calcium should be measured on the first post-surgical day and should be continued until discharge (193, 195, 199, 200). If hypoPT is present three guidelines give information regarding the medication (195, 199, 200) while one guideline (191) refers to the American (203) guideline for the management of hypoPT. For the management of permanent hypoPT the guidelines (191, 193, 199) who address this topic are with their recommendations in line with the guidelines for the management of hypoPT (176,

203) namely that laboratory parameters should be checked at least every six months in order to adjust medication. Additionally, these guidelines are in line with the recommendation that on a regular basis efforts should be undertaken to wean of the calcium and/or vitamin D medication (176, 203). Finally, two guidelines recommend that the management of post-surgical hypoPT after TC should lie in the hands of a specialist and not the general practitioner (199, 201). No guideline for the management of TC addresses the impairments in QoL that come alongside with post-surgical hypoPT in a sufficient way.

The German S2k guideline for the surgical therapy of benign thyroid diseases (187) should be highlighted even though it is not related to TC. In this guideline all important information regarding post-surgical hypoPT are mentioned even with focus on QoL. It also does promote an emergency card for patients with hypoPT in order to inform physicians about the disease. Norwegian hypoPT patients did rate this emergency card very relevant for their disease because it helps reducing the numbers of emergency department visits or hospitalizations due to hypocalcemia (204). In Germany the emergency card is available at the Netzwerk Hypopara (205).

When looking at guidelines or consensus statements for the management of hypoPT Qol of the patients always plays an important role. Both the European (176) and American (203) guideline state the good QoL should be main goal of the treatment for hypoPT and not reaching normocalcemia. The topic of TC is not explicitly addressed in these guidelines.

11.2 Follow-up of thyroid cancer patients

As seen in Section 9.1 heterogeneity between the guidelines exist and few recommendations regarding follow-up and postsurgical hypoPT are available. Therefore, the question arises how follow-up of TC patients in Germany and on international levels is performed, and how quality of life and post-surgical hypoPT is addressed in clinical practice.

11.2.1 Follow-up of thyroid cancer patients

Guidelines recommend that the follow-up of TC patients should be performed by a specialist (199, 201). Results from a patient survey indicated that the majority (53.6%) of TC patients in Germany is treated during follow-up by a nuclear medicine specialist, followed by an endocrinologist or endocrine surgeon (19.9%), 7.1% by another specialist and 3.1% by an oncologist. Almost every fifth patient (16.2%) is being treated by their general practitioner (206). There was a statistically significant difference regarding the treating physician if patients were diagnosed with chronic hypoPT after TC compared to the patients without. While the nuclear specialist still treats the majority of patients (hypoPT: 52.5%, non-hypoPT: 57.2%), the share of endocrinologists (hypoPT: 32.3%, non-hypoPT: 17.0%) and the general practitioners (hypoPT: 13.3%, non-hypoPT: 19.2%) do differ. The same study also asked TC patients from

France, and there the follow-up is differently organized. While the majority of patients are treated by an endocrinologist or endocrine surgeon (63.3%), only a few patients are treated by a nuclear medicine specialist (9.6%). With 16.3%, the share of general practitioners being responsible for the treatment is as high as in Germany. The same pattern as in Germany can be seen for the comparison of hypoPT and patients without hypoPT. The share of endocrinologists being responsible for treatment is statistically significantly higher in the hypoPT patients group (hypoPT: 74.3%, non-hypoPT: 51.9%) (206). In a patient survey from 2013 by Banach et al. (207) that included 2398 patients from mainly 5 countries (US (37.9%), Germany (21.3%), the UK (11.5%), Canada (11.4%), France (9%), and 35 other countries), follow-up care was mostly performed by endocrinologists (53.3%), nuclear medicine specialists (14.9%), and oncologists (11,9%). Surgeons (4.6%) and other specialists (15.9%) played a minor role. In a Canadian study by Bender et al. (208), 202 TC survivors reported that their follow-up care was managed by a surgeon or oncologist (82.5%). In a study by Hudson et al. (209), 52% of the participants shared the opinion that thyroid cancer survivors should see a specialist for regular follow up because they had the feeling that their general practitioner was ignoring the cancer-related problems. Regarding the number of follow-up visits per year, no clear recommendations are available. In the study by Bender et al. (208), patients reported a median of three follow-up visits per year. The overall satisfaction with the management of TC among patients is good (210). Surgeons (69.1%), oncologists (64.3%), and endocrinologists (64.0%) received the highest share of high satisfaction by the patients.

11.2.2 Follow-up and management of post-surgical hypoparathyroidism in thyroid cancer patients

The follow-up and management of TC patients with post-surgical hypoPT starts on the day after surgery by measuring PTH and calcium levels and assessing hypocalcemic symptoms (187, 199, 211-214). Except for the study (172) included in this thesis, we do not have much published information regarding the assessment of PTH and calcium levels after surgery for TC in Germany. In our study, all patients who had surgery for TC at the University Medical Centre Mainz between 2010 and 2015 had their blood parameters checked within 24 hours after surgery. Of the 421 patients who had surgery, 134 (31.8%) had a parathyroid hormone level below 20 ng/l and/or serum calcium level below 2.1 mmol/l within 24 h after surgery for thyroid cancer and were then treated with calcium and/or vitamin D. Of the 75 patients for whom full data was available, 36 (48%) were still taking calcium or vitamin D medication one year after hospital discharge, but only 4 self-reported a diagnosis of hypoPT. We were not able to determine whether medication was not tapered off in the remaining patients or whether they were not aware of their hypoPT diagnosis. Leidig-Bruckner et al. (215) reported that 33 (20.1%) of 164 MTC patients were discharged with hypoPT after surgery. Of these, 13 remained with chronic hypoPT while hypoPT was only transient for the rest. The authors did not report on

whether any attempts were undertaken to taper off the medication, but they state that the use of calcitriol increased from 33% at hospital discharge to 72.7% at the end of the study. In a subgroup analysis of the online survey used for Paper 3 (173), 32 (32%) of the 100 hypoPT patients where TC was the cause of the disease reported that a least one attempt was undertaken to taper off the supplementation (64% “never” and 4% “don’t know”). Another German paper (216) investigating the situation of post-surgical hypoPT after TC was retracted due to mistakes in data collection (217), resulting in very little information for Germany. A larger study by Benmiloud et al. (98) found that of 898 patients with undetermined parathyroid status after surgery for TC, 365 were still treated with calcium and/ or vitamin D one year postoperatively. According to the fifth national audit of the British Association of Endocrine & Thyroid Surgeons (BAETS) (218), 40% of patients who had thyroid surgery are on calcium and/or vitamin D supplementation at hospital discharge. A small proportion (2.2%) of patients with hypocalcemia did not receive any supplementation, while on the other hand 15.6% did receive calcium and vitamin D supplementation without developing hypocalcemia. Of the surgeons who reported not giving supplementation, 70% stated that they do so selectively on an individual patient basis while the rest does this universally. This reflects the variation in British surgeons in dealing with post-surgical hypoPT which has also been reported in another British study. Htun el al. (219) assessed the management of post-surgical hypoPT in nine NHS Trusts in North-West England and found that all hospitals performed at least one postoperative check of calcium and PTH levels, but only seven of the nine perform a second check prior to discharge. Four of the nine hospitals performed a check 48-72 hours after surgery in order to exclude a delayed onset of hypoPT. The authors state that there is variation in the management of post-surgical hypoPT in England due to a lack of regional and national consensus on how to approach this topic. Regarding the follow-up of permanent hypoPT after TC, to our knowledge no studies are available that solely focus on permanent hypoPT after TC but on hypoPT populations with mixed causes. The available studies (174, 206, 220-222) report that the majority of patients with permanent hypoPT have their blood parameters checked at least every six months as recommended by the respective guidelines (176, 203). Büttner et al. (222) reported that in their study of 264 hypoPT patients, 73.8% had their serum calcium levels checked at least every six months. Lower percentages were reported for checks at a 6-month interval for phosphate (46.9%), magnesium (36.3%), creatinine (53.6%), and parathyroid hormone (49.6%). In a subgroup analysis of the sample, TC patients had lower 6-month check frequencies compared to non-surgical cases or cases with surgery for benign disease for calcium (TC: 67%, non-surgical: 90.5% and benign: 79%), phosphate (TC: 39%, non-surgical: 42.9% and benign: 52.4%), and PTH (TC: 41%, non-surgical: 52.4% and benign: 54.5%). For magnesium (TC:33%, non-surgical: 33.3%, and benign: 38.5%) and creatinine (TC: 52%, non-surgical: 47.6%, and benign: 54.5%), TC had approximately the same timing

for checks. It is not known if patients in the TC group had one specialist for the follow up of TC and hypoPT or if this was performed by different specialists. Rates of 75% or higher for 6-month calcium checks in mixed hypoPT populations have also been reported by Hadker et al. (174), Allemeyer et al. (220) and Hamdy et al. (221).

11.2.3 Assessment of quality of life in thyroid cancer patients in clinical practice

Literature where QoL assessments in TC patients have been implemented into clinical practice is scarce. Gamper et al. (223) report on the implementation of a QoL monitoring program at the nuclear medicine department of the Medical University Innsbruck. From 2005 to 2013, 439 TC patients filled out the EORTC QLQ-C30 at least once during a visit at the department. Two-hundred eighty-four (64.7%) questionnaires before and after radioiodine treatment were available measuring impairments in QoL that could then be discussed with the treating physician. To our knowledge no other studies have been published that report on the implementation or assessment of QoL of TC patients' QoL in clinical practice. Cramon et al. (45) at least provide an overview of what is needed if QoL in TC patients is be assessed in clinical practice. That QoL assessment is also relevant in follow-up has been expressed by patients. In the large patient survey by Büttner et al. (206), 41.4% of the German participants (France: 35.6%) have changed their treating physician at least once. The most frequent reasons for changing the treating physician were feeling inadequately treated (Germany: 28.5%; France: 35.0%), or the feeling that quality of life issues were not addressed (Germany: 21.1%; France: 35.8%). In this sample, postsurgical hypoPT had no impact on the reason for changing the physician. No studies regarding the measurement of QoL in clinical practice in hypoPT are available, even though from personal experience some clinics in Germany (e.g. MVZ Göttingen) use the HPQ-28 in clinical practice for the assessment of hypoPT symptoms.

11.2.4 Unmet information needs of thyroid cancer patients with and without hypoparathyroidism

The unmet information needs of TC patients are multifaceted. As seen in the previous section, the biggest lack of information is in follow-up and aftercare. Husson et al. (224) showed that 86-91% of TC survivors feel that they receive no or little information regarding aftercare. That lack of information in aftercare can be found in different areas. Receiving psychological support is one of the dominant information needs of TC patients and survivors (206, 207, 210). Since psychological well-being is an aspects QoL, this information need addresses QoL (65, 225-228). In Germany, patients with rarer cancers (including TC) are the ones receiving the least psycho-oncological support (207, 229, 230). Even though psycho-oncological support is part of national cancer plans (231) and highlighted in guidelines and studies (188, 191, 195, 199, 232-234), there still seems to be a lack of these services. Other information needs stated by TC patients are more information regarding the disease or information about self-help groups.

Treatment side effects, which might include hypoPT, are also stated by high shares of patients (206, 207). At the time of diagnosis, German TC patients stated that they did not receive any information regarding psychological support (79.2%), self-help groups or organizations (76.9%), and regarding the disease and the treatment (61.4%) (206). When TC patients receive information, there is also a big discrepancy regarding the satisfaction with the provided information. While patients are often satisfied with the information regarding diagnosis and primary treatment, less satisfaction is observed for information regarding long-term effects, recurrence, and aftercare (224, 235). In a study by Diez et al. (210), high levels of dissatisfaction with the information received were seen for psychological support (69.4%), treatment of other complications (55.7%), and treatment of hypoparathyroidism (45.4%). Patients with hypoPT after TC report additional information needs. In a study by Büttner et al. (222), 40.6% of the patients stated that their treatment for hypoPT was not adequately explained to them, and 25% reported that they did not receive any information regarding hypocalcemia. These findings are in line with findings from a mixed hypoPT population from Norway (204). Patients with hypoPT after TC report additional information needs regarding long term effects of treatment, new therapies, and the disease itself (222). Overall it can be observed that improvements in providing information for TC patients with and without hypoPT is necessary.

11.3 Electronic patient-reported outcomes for the assessment of quality of life in thyroid cancer patients

As seen in Section 9.2.3, QoL assessments in TC patients in clinical practice are not common. The assessment of PROs brings various advantages for patients and clinicians, such as better patients-physician communication (236-238), higher patient satisfaction (236, 239-241), closer monitoring of symptoms (238, 242-245), better shared decision making (239, 244, 246), increased QoL itself (238, 245, 247-249), and improved survival (243, 245, 247, 250, 251). On the other hand, various barriers such as being unfamiliar with the concept of QoL (237), time constraints (252-254), interpretability of the QoL scores/ results (252, 253), and costs (255, 256) exist. When using electronic patient reported outcomes (ePROS), some of the barriers can be reduced to a minimum or even become completely irrelevant. With ePROS, the time to analyse the questionnaire used is reduced to seconds and the results are available to the physician also within a short time frame, making them applicable even in clinical practice where time may be short (223, 257-259). The interpretability of QoL scores is enhanced when using ePROS (260). Various options (e.g. graphs charts, numbers) can be applied to best fit the person interpreting or communicating the results (261, 262). Using cut-offs for clinically important differences enables physicians to quickly identify areas of QoL or symptoms that should be addressed (263). One of the most often used arguments against PROs/ ePROs in clinical practice is the cost for the implementation and use of such an assessment (255, 256).

Nevertheless, Lizée et al. (264) have shown that ePROs are cost-effective in lung cancer patients. Patients in the intervention arm filled out a 12-item symptom questionnaire every week while the control arm received standard of care. At every follow-up visit the results of the questionnaires were available for the treating physician and whenever a severe decline in QoL was detected, an alarm was triggered for the treating physician. Even though the implementation of the ePRO system was quite costly, it was still very cost-effective. Annual follow up costs in the intervention arm (€941) were statistically significantly lower compare to the control arm (€1304). Nixon et al. (265) also confirmed the cost-effectiveness of a web-based QoL instrument in the management of patients with advanced or metastatic cancer in Alberta, Canada. The problem with results like these are the different payers' perspectives. While the hospital or the treating institution has to bear the costs of implementing and maintaining the ePRO system, the monetary benefits of such an implementation are located on the payers' side (e.g. insurance, state, patient). Therefore, reimbursement schemes need to be developed that make the implementation of such systems meaningful for all stakeholders involved (266). Another concern regarding ePROS is that they might exclude certain patient groups (e.g. older patients, patients with low technical knowledge) but various recent studies have shown that this risk is not as high as a decade ago (267, 268). Additionally, the question exists whether ePROs provide the same results as the classical pen and paper versions of questionnaires. Recent studies have shown that there are no differences in results regarding the form of administration and that ePROs indeed have a high acceptance in cancer patients (260, 269-271). With all the advantages of the assessment of QoL in clinical practice using ePROs, the question arises as to why it is rarely implemented in TC patients (45, 223) while in other cancer populations more successful implementations have been reported (245, 247, 258, 259, 272, 273). There are various possible explanations for this finding. First, thyroid cancer is still considered by some physicians as "a good cancer", therefore neglecting the severity of the disease and the impairments in QoL. In a study by Papaleontiou et al. (274), of the 448 (42% endocrinologists, 30% general surgeons and 28% otolaryngologists) participating physicians, 49% told their patients that thyroid cancer is "a good cancer". In James et al. (275) this number was even higher, with 54% of the physicians telling their TC patients that it is a "good cancer" or the "kind of cancer to get if you have to get cancer", with no statistically significant differences with regard to profession (surgeons vs. medical physicians). Another possible reason for the low implementation rates of ePROs in clinical practice of TC patients might be attributable to the rarity of the disease (1). In more common cancer types, the health and financial impact might be rated higher, driving a focus on these cancer types. Thirdly the lack of TC-specific tools might have had a negative impact on the implementation in the past. With the new EORTC QLQ-THY34 (54) and the ThyCAQOL (55), two tools are now available that can be combined with cancer-specific tools in order to best assess TC patients' QoL, making it usable

in clinical practice. In a study by O'Neil et al. (276), only around 40% of the participants stated that generic questionnaires (38% for the SF-12 and 42% for the EORTC QLQ-C30) fully captured their disease experience. These numbers rose to 54% (ThyCaQol) and 52% (COH-TV) respectively when a TC-specific tool was used. Nevertheless, these numbers are still quite low and might also be attributable to the fact that these tools are not able to cover the broad spectrum of symptoms (167, 173) which, for example, are experienced by hypoPT patients. One last argument of the low implementation rates might be the high demands regarding data protection in order to establish ePROs and the inability to exchange data between professions and institutions (277-279). This barrier is not only related to TC but to all cancer types.

12. Conclusion

As seen in the papers used for this thesis accompanied by findings from the literature, it is very likely that patients with post-surgical hypoPT after TC report higher impairments in QoL compared to TC patients without hypoPT. In order to address these impairments, psychological support and adequate information regarding treatment risks (including hypoPT), potential impairments in QoL, and opportunities for support (e.g. psycho-oncologist, self-help groups) should be made available to the patient. The assessment of QoL in clinical practice using ePROs might also help to reduce the burden caused by TC and/or hypoPT. If hypoPT is confirmed, the use of an emergency card can be considered by the patient. This card holds all relevant patient and disease information so that in event of severe hypo- or hypercalcemia, the treating physicians can quickly make adequate decisions. Patients have shown a high satisfaction with this card, and it also has been shown that the card has the potential to reduce hospitalizations of hypoPT patients. Considering the burden and impairments of TC patients with or without hypoPT, health care providers should keep in mind that it is not appropriate to call TC "a good cancer" or "the kind of cancer to get if you have to get cancer" as it has happened sometimes in the past.

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Wissenschaftliche Qualifikation

Publikationen: 32 (Stand: Dezember 2023)

Ausgewählte Publikationen

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