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Guideline

Consensus statement of the European Society of Endocrine Surgeons (ESES) on advanced parathyroid cancer: definitions and management

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Introduction

Parathyroid carcinoma is extremely rare, ranking among the rarest of all malignant tumours with a ratio of 0.005%[1–3]. The condition can be fatal, with limited systemic treatment options. The rareness of the disease is matched by the scarcity of literature on parathyroid carcinoma[4]. A bibliometric analysis[5] including data from the past 22 years identified just 3578 articles, with a majority focusing on differential diagnosis, gene mutations, and local recurrence.

Experience in managing parathyroid carcinoma, especially advanced cases, is limited even in large endocrine surgical centres. Owing to the low incidence, no level I–III evidence on the management of advanced parathyroid cancers is available, nor any established standards on the surgical approach and adjuvant options[6]. There is, moreover, great heterogeneity in the literature, especially when it comes to surgical techniques. Agreement on how to manage patients with advanced cancers has been difficult to achieve because of lack of prospective evidence from RCTs. Conversely, consensus-based treatment plans are used in rare disease to reduce diversity in treatment modalities. This is of significant benefit for the management of parathyroid carcinoma as well, as there are currently insufficient high-quality evidence-based guidelines and data.

The European Society of Endocrine Surgeons (ESES) has dedicated the 2023 ESES conference to discussing the management of advanced endocrine malignant tumours. This paper summarizes the current knowledge and discusses areas of uncertainty related to the management of advanced parathyroid carcinoma. Discussions related to diagnostic issues are outside the scope of this article.

Methods

Working group composition and literature search

The Advanced PArathyroid CAncer WOrking Group (APACAWOG), a working group established by the ESES and composed of endocrine surgeons who are ESES members, conducted the present collaborative work to form a positional statement for management of advanced parathyroid carcinoma. The group held bimonthly virtual meetings and met at annual ESES meetings (conferences and congresses).

A thorough and methodical search was carried out to identify medical literature released between March 2010 and March 2023 by two independent groups of four investigators in parallel. PRISMA guidance was applied to collate studies from PubMed (MEDLINE), Embase, Scopus, and the Cochrane Library with the Medical Subjects Headings (MeSH) 'parathyroid cancer' OR/AND 'parathyroid carcinoma'. Using Microsoft® Excel 2019 (Microsoft, Redmond, WA, USA), each of the four reviewers independently extracted data from the chosen articles in each group. When conflicts arose during article selection and data extraction processes, they were settled by arbitration by a third reviewer or by consensus. Owing to a lack of randomized controlled and prospective studies, individual case reports, case series, and observational studies were also included. Animal studies, expert

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opinion manuscripts, letters to the editor, commentaries, conference papers, and studies regarding laboratory, genetics and mutations were excluded. Management of advanced parathyroid cancers was the outcome that attracted particular attention.

Panel composition, modified Delphi process, and voting

The literature review informed the development of a structured multiple-choice survey designed using the Delphi method. This survey was first sent first to all members of the APACAWOG. After each round, the facilitator collected the answers and opinions of the team that was blinded to this part. A structured survey was created after the core questionnaire had been verified, in accordance with the responses obtained. The online Qualtrics® software link (www.Qualtrics.com, Provo, Utah) was used to administer the 13-question survey.

Senior ESES members, with at least 6 years of experience in endocrine surgical practice, were chosen at random and invited based on their qualifications. This included working at a tertiary reference hospital with a comprehensive endocrine disorders treatment facility for at least 5 years, dealing with endocrine patients for at least half of their daily clinic time, and attending regular multidisciplinary tumour board meetings every week for at least 5 years. The authors also approached members who were active on the European Union of Medical Specialists (UEMS) Board of Endocrine Surgery. Correspondence with these members was done by e-mail. All members expressed a willingness to participate and 100% responded. In the third round, to clarify and finalize the scant data available in the literature, the views of the above senior group were collected anonymously, and the survey design was finalized before validation. The answers of these groups (ESES senior members and UEMS Board of Endocrine Surgery members) were similar to each other and supported the validation process. The final validation was based on consultation with two senior biostatisticians to set the criteria and feasible number of questions.

Draft statements were generated by APACAWOG members using data derived from the literature review, the survey, and the European Registry for Endocrine Surgery (EUROCRINE®). Key questions/recommendations were prepared and presented by the moderator during a plenary session at the 2023 ESES conference. A short time for discussion was permitted for input from the conference delegates, and all delegates present were asked to vote. For voting, a standard validation analysis with approximately 100 attendees was accepted to be sufficient. A Likert scale from 1 (strongly disagree) to 5 (strongly agree) was used for voting on each question. Three categories were created from the outcomes of each recommendation: disagree (1–2), abstain from voting (3), and agree (4–5). For agreement, at least 80% was required, with less than 10% negative votes. 'Consensus not reached' was applied when a vote failed to garner a quorum or meet the requirements for a decision. Outliers were defined as any value at least 1 Likert point away from the mean. For 13 specific recommendations, the consensus process was deemed complete once the thresholds had been reached in any round. The outcomes of each voting are provided as descriptive variables. There were situations where conference delegate responses were almost evenly divided, either owing to missing evidence or different personal treatment priorities (for example conservative *versus* more aggressive approach). This could speak in favour of mutually exclusive treatments, and so the treatment corridors proposed are shown here in a manner that even seemingly contradictory treatment concepts are considered acceptable options (for example statements 6 and 13).

EUROCRINE®

Studies of rare tumours, such as parathyroid carcinomas, take advantage of multicentre collaborations with standardized databases. EUROCRINE®, which is an online endocrine surgical quality registry that seeks to reduce mortality in the surgical care of patients with endocrine tumours, with a special focus on rare tumours, was used[7]. Departments/clinics begin entering data on EUROCRINE® as soon as the legally accountable hierarchy has signed the consent form enabling them to use the data, and the registry is open for all countries to join. Entering data is not obligatory. At local hospital level, as well as at overall national and supranational level, data are collected to analyse diagnostic processes, indication for surgical treatment, types of surgical procedure, use of resources, and outcomes. Evaluation of compliance at national level is the responsibility of the EUROCRINE® board members. The search was restricted to patients who had been registered between 2015 and 2022, and who underwent surgery for parathyroid carcinoma. Each centre performed the procedures according to its protocol. Preliminary outcomes were also presented during the 2023 ESES conference.

Finalization of position statement and organizational approval

After the workshop, the manuscript was further revised by members of APACAWOG. A decision was taken to publish a synopsis of the recommendations as a consensus statement of the ESES. The quality of evidence for each statement was stratified as high, moderate, low, and expert opinion, depending on the type of publications that data were extracted from. High-level evidence referred to data stemming from RCTS, moderate-level evidence was derived from non-randomized prospective trials, and low-level evidence from retrospective analysis or case series. Where no supportive data were available, the term 'expert opinion' was used. A summary of the statements is presented in *Table 1*.

Results

Outcome of literature search, original draft, and statement production

With date and language filters, there were 1212 citations for the set inclusion criteria when the Rayyan tool was adopted[8]. Reference lists of included studies were searched for potentially relevant studies and, if identified, imported into Rayyan for screening. The reason for exclusion was documented. The search for advanced parathyroid cancers identified 148 publications, of which 57 met the selection criteria. Thirty-one articles were eliminated because of potential duplicate use of data, or lack of information on follow-up, outcomes, or treatment of advanced disease. The pooled analysis finally contained data from 26 publications (*Fig. 1*).

Incidence

According to estimates, parathyroid carcinoma causes hyperparathyroidism in 0.017–5.2% of cases in Europe, the USA, and Japan. Several series[9–12], however, have indicated that this entity accounts for less than 1% of patients with primary hyperparathyroidism. It has been proposed recently that, during the previous 40 years, there has been an increase in the incidence of parathyroid carcinoma. Lee *et al.*[13] have shown that there has been a 60% rise in the incidence of parathyroid carcinoma, with 3.58–5.73 cases per 10 million patients. Whether this trend has persisted since the analysis by Lee *et al.* is unknown. According to Lo *et al.*[14], since 2001, the incidence has stabilized at 11 cases per

Table 1 Summary of European Society of Endocrine Surgeons statements for management of advanced parathyroid carcinoma

Statement		Level of evidence
1a	Parathyroid carcinomas classified as at least T2 (direct invasion into the thyroid gland) according to the AJCC 8th edition have to be considered locoregionally advanced tumours Consensus: Yes (85%), Outliers: 6%	Expert opinion
1b	In the presence of distant metastasis, parathyroid carcinomas have to be considered advanced, independently of locoregional status Consensus: Yes (85%), Outliers: 6%	Expert opinion
2	If parathyroid cancer is suspected on clinical and biological grounds, together with ultrasound imaging and sestamibi scintigraphy and/or SPECT–CT, contrast-enhanced CT and/or MRI to investigate local invasiveness, and [^{18}F]FDG PET and/or choline PET and/or ^{99m}Tc sestamibi SPECT–CT to investigate functionality and presence of distant metastasis, should be preferred Consensus: Yes (94%), Outliers: 6%	Low
3	There is no role for biopsy in patients with suspected parathyroid carcinoma Consensus: Yes (92%), Outliers: 4%	Low
4	*En bloc* resection, including the thyroid lobe and peritumoral/perithyroid tissue, avoiding capsular rupture, is recommended in patients with T1 parathyroid carcinoma Consensus: Yes (94%), Outliers: 4%	Low
5	Centres with experienced endocrine surgeons that perform > 40 parathyroidectomies a year, dealing with locally advanced thyroid cancer, and that can provide both intraoperative and postoperative (adjuvant or palliative) support from other specialties should perform parathyroid cancer surgery Consensus: Yes (88%), Outliers: 4%	Low
6	A functioning recurrent laryngeal nerve with EMG signals proximal to the infiltration site should be managed conservatively, and disease clearance should be achieved while maintaining structural and, ideally, functional integrity of the nerve Consensus: No (31%), Outliers: 33% Conclusion: A wide treatment corridor in regard to surgical decision-making for preserving or sacrificing a recurrent laryngeal nerve infiltrated by parathyroid carcinoma is proposed. In the event of entrapment of the recurrent laryngeal nerve—but preserved function as demonstrated via intraoperative neuromonitoring by EMG signals proximal to the infiltration site—the surgeon must decide between the mutually exclusive priorities of R0 resection on the one hand or preservation of nerve function on the other hand, which are both acceptable until newly emerging data show an advantage of one option	Low
7	In patients with limited (stage I or limited stage II according to Shin classification) involvement, tracheal shaving should be performed. In those with extensive (stage III or IV) involvement, tracheal resection and/or two-stage resectional surgery (following previous conservative surgery and adjuvant treatment) should be considered according to multidisciplinary team goals of care and patients' preferences Consensus: Yes (86%), Outliers: 2%	Low
8	In patients with oesophageal involvement that does not extend into the lumen, only the involved musculature should be resected. When local disease control requires full-thickness excision and reconstruction, surgical options should be based on multidisciplinary team goals of care and patients' preferences Consensus: Yes (94%), Outliers: none	Low
9	Locoregionally advanced parathyroid carcinoma does not require four-gland exploration in case it is sporadic. Familial cases may need bilateral exploration Consensus: Yes (86%), Outliers: 6%	Low
10	Cytoreductive surgery is of interest in terms of life expectancy. A non-R0 surgical resection can reduce hypercalcaemia and improve quality of life Consensus: Yes (80%), Outliers: 20%	Low
11	When cytoreduction is believed not to be sufficient to reach adequate calcium and PTH level reduction, by evaluating patient condition and view, a multidisciplinary team decision should be taken Consensus: Yes (80%), Outliers: 19%	Low
12	Regarding intraoperative adjuncts, nerve monitoring is recommended during advanced parathyroid carcinoma surgery Consensus: Yes (86%), Outliers: 11%	Low
13	Parathyroid carcinoma is known to be radioresistant and the impact of radiotherapy in the adjuvant setting is not known. The use of radiotherapy may be considered with a multidisciplinary team decision and may have value for palliative reasons Consensus: No (20%), Outliers: 40% Conclusion: A wide treatment corridor in regard to the role of radiotherapy in advanced parathyroid carcinoma is proposed owing to the scarcity of evidence. Decisions by a multidisciplinary team for or against radiotherapy for a patient are both considered acceptable until newly emerging data show an advantage of one treatment option	Low

SPECT, single-photon emission CT; [^{18}F]FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; EMG, electromyographic; PTH, parathyroid hormone.

10 million people. The incidence has stayed steady rather than rising in the following years . Additionally, a subgroup analysis of prognostic factors revealed that regional disease (locally invasive and lymph node-positive disease) and smaller tumours (less than 3 cm) account for the majority of the increasing incidence. This implies that improved routine calcium screening and surgeon referral for parathyroidectomy may be the reason for the previously noted increase in incidence[13,15].

Staging

Parathyroid cancer is typically staged based on whether the primary tumour is confined to the parathyroid gland, is extraglandular, or associated with distant metastases. The number of lymph node metastases or tumour size has not been found to have significant predictive value. Some additional prognostic factors[16–18] that have been discovered in previous population-based studies is covered in a related section of this

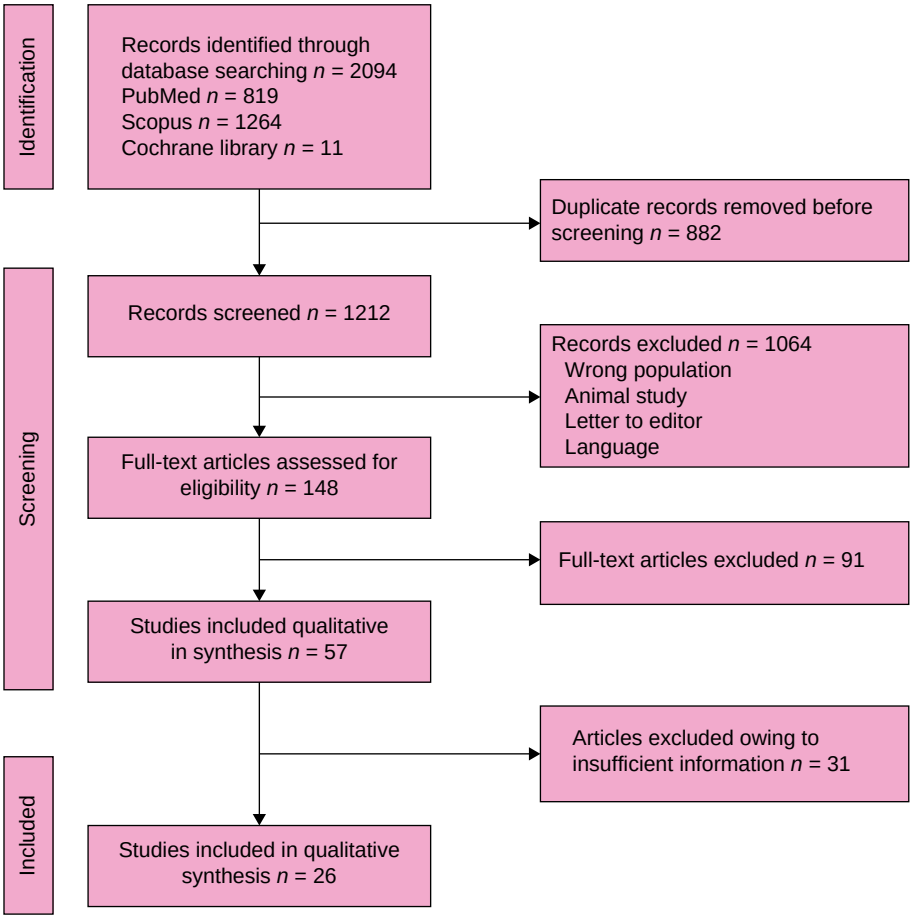

Fig. 1 Flow chart showing selection of articles according to PRISMA statement

work. Until 2017, there was no established staging system in place, although some have been suggested[2,19]. The AJCC planned to stage parathyroid carcinoma in the 8th edition of the AJCC Cancer Staging Manual for the first time in 2017. The degree of invasion or regional lymph node involvement is unclear owing to a paucity of data on its value as a significant prognostic factor for parathyroid carcinoma. Moreover, studies have been inconsistent regarding the prognostic significance of tumour size. Only T, N, and M categories were established, but no cancer stages were defined[20]. The purpose of the suggested staging system is to consistently collect data that will aid in future staging optimization. The only constant factor in the literature that is thought to be predictive of overall survival is the existence of distant metastases. Roser *et al.*[21] recently proposed a staging system based on the 8th edition of the AJCC TNM staging: stage I as T1 or T2 N0 M0; stage II as T3 N0 M0; stage III as any T N1 M0; and stage IV as any T any N M1.

Initially, Shaha and Shah[19] modified the TNM staging system by adding macroscopic factors, such as tumour size and invasion into other tissues. According to Xue *et al.*[22], however, this TNM system was not predictive because increased disease stage did not indicate worse prognosis. The modified system of Talat and Schulte[2] surfaced, and included additional patterns of local tumour invasion into other organs. This classification did not predict mortality, but it did identify groups of patients with parathyroid carcinoma who were at high risk of death and recurrence. A prognostic scoring system that allows patient stratification based on variables that are available in the early postoperative course was proposed by Silva-Figueroa *et al.*[23]. A high-risk category was defined, namely those over 65 years old with preoperative serum calcium levels greater than 15 mg/dl and tumours exhibiting vascular invasion; these may be candidates for increased surveillance. They also proposed that adjuvant treatment and additional oncological resections should be taken into account for this high-risk group.

Definition of advanced parathyroid cancer

In the event of local tumour invasion into adjacent anatomical structures, decision-making during surgery becomes challenging. In parathyroid cancer, extent, invasiveness, and distant spread have been associated with the presence of one, or the combination of two main features: locoregional and distant metastatic disease. The features are defined indirectly in the 8th edition of the AJCC Cancer Staging Manual[20]. As mentioned above, staging is still lacking and the focus of this system is mortality, instead of portraying with accuracy a complex issue such as advanced parathyroid disease. To better capture this concept, disease-specific morbidity as well as the surgical and non-surgical challenges present when managing such patients should be taken into consideration. Nevertheless, the TNM classification is the most widely recognized and used system globally, and in that sense, any major deviations from its application when defining advanced disease might render any new definition impractical for everyday clinical and research use. The TNM staging system does not, however, take into account certain factors that have been linked to parathyroid cancer, such as age, serum calcium levels, intact parathyroid hormone (PTH) levels, vascular invasion, local excision, tumour size, and lack of parafibromin staining[15,23–25]. The

TNM staging strategy for parathyroid cancer has also been questioned in light of several reports addressing the importance of tumour size[2,14,26,27]. As a result, TNM staging is somewhat deficient and cannot accurately predict the prognosis of individual patients with parathyroid cancer.

Locoregionally advanced disease was found in 22.5% of 134 patients with parathyroid cancer whose data were evaluated and entered into the EUROCRINE® registry between January 2015 and December 2021. Eleven patients (8%) had distant metastases (unpublished data). Data on parathyroid carcinoma, extracted from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed between 1975 and 2016, revealed that 25.2% of patients had regional metastases, and 2.2% had distant metastatic disease[28]. According to a more recently published retrospective SEER analysis of 407 patients carried out by Sun *et al.*[26], thyroid invasion, which the AJCC uses to determine the T1 and T2 staging criteria for parathyroid carcinoma, had no effect on the prognosis of patients without local lymph node metastases or distant metastases. They suggested that tumour size of at least 4 cm could be a reliable predictor of T1 and T2 cancer stage. Another retrospective review[14] of the SEER database between 1973 and 2014 was undertaken, which included 520 patients with parathyroid carcinoma. In this study, most patients presented with either local (67%) or regional invasive (31%) disease. Several prognostic factors linked to extended disease-specific survival were examined. The extent of the cancer and tumour size greater than 3 cm were linked to lower cancer-specific survival in both univariable and multivariable analyses. In contrast to patients with distant metastatic disease, whose median survival was only 2.5 months, those with local or regional disease, including locally invasive and lymph node-positive disease, did not reach the median survival. In terms of disease severity, Çalapkulu *et al.*[29] suggested tumour volume to be a more effective parameter than tumour size.

Although the results for patients with early-stage parathyroid cancer have been the subject of numerous publications, little is known about the prognostic factors and treatments for patients with advanced disease. Multiple surgical interventions with debulking of tumour tissue along with medical treatment to reduce hypercalcaemia may be required because parathyroid cancer is an indolent tumour associated with possible long-term survival, and death can also be due to complications of untreatable hypercalcaemia[3]. The report of a large European series by Schulte *et al.*[6] emphasized the importance of negative margins and radical oncological resection in parathyroid carcinoma. This series of 25 patients demonstrated the long-term benefits of an oncological *en bloc* R0 surgical approach; the disease-specific survival rate was 100% over a 10-year interval. Extended surgery was found to lower recurrence rates, based on univariable analysis of 83 patients from a European retrospective multicentre study (NEKAR). This study also suggested that lymph node dissection had no value[30].

An increased risk of all-cause mortality with an unknown degree of disease was indicated in a model by Allen *et al.*[31]. Unknown disease extent could be used as a proxy for locally advanced but difficult-to-measure illness. One would, however, have expected it to also have indicated a worse prognosis for the illness and a particular survival rate, which was not observed.

Non-functionality is another factor with an impact on progression. Non-functional parathyroid carcinomas are much less common, accounting for between 10 and 25%[32–34]. These tumours typically manifest late and at an advanced stage because they do not show any symptoms[35]. They are associated with hoarseness, fixation to the surrounding structures, and a large palpable mass as locally invasive symptoms. In decreasing order, the thyroid, strap muscles, oesophagus, recurrent laryngeal nerve, and trachea are surrounding structures that are implicated[36].

Definition of locoregional disease

Statement 1a: Parathyroid carcinomas classified as at least T2 (direct invasion into the thyroid gland) according to the AJCC 8th edition have to be considered locoregionally advanced tumours
Consensus: Yes (85%)
Outliers: 6%
Evidence level: Expert opinion

Owing to the rarity of the disease, and based on the responses to the survey, it was decided not to differentiate between locally advanced and regionally advanced, and merge the two terms into a single category as locoregionally advanced. Published data revealed that parathyroid carcinoma tends to spread more by local extension than lymphatic channels[37]. A locally advanced situation in parathyroid cancer may be associated with a worse prognosis. Morbid sequelae of local invasion, such as recurrent nerve, tracheal, and/or oesophageal invasion, are involved in disease-specific causes of morbidity. Fortunately, these locally infiltrative tumours are extremely rare.

As mentioned previously, it is unclear whether a parathyroid tumour invading the thyroid affects the prognosis of patients without lymph node or distant metastases. Kong *et al.*[15] reported that combined thyroidectomy at initial surgery was a significant prognostic factor for survival. Based on the current findings, it has been stated that a patient's prognosis and outcome depend greatly on the extent of the initial resection[18,38].

As study findings have been inconsistent and the prognostic significance of extent of invasion or regional lymph node involvement is unclear, there has recently been a lack of encouraging data regarding disease-specific survival. As such, only T1 tumours, localized to the parathyroid gland with extension limited to soft tissue, can be omitted from the definition of locoregionally advanced cancer. The relationship between the tumour and the thyroid gland should be considered carefully, because the parathyroid glands as well as their neoplasms are located predominantly adjacent to the thyroid but occasionally also inside the thyroid[13]. This feature can be considered as a flaw in the recently proposed AJCC staging system, which uses this characteristic as a yardstick for upstaging parathyroid carcinoma[39].

Furthermore, it has been found that locally infiltrative carcinomas with positive staining results exhibit better biological behaviours than carcinomas lacking parafibromin expression in analyses of clinicopathological features with metastasis and parafibromin staining[40].

Metastatic disease

Statement 1b: In the presence of distant metastasis, parathyroid carcinomas have to be considered advanced, independently of locoregional status
Consensus: Yes (85%)
Outliers: 6%
Evidence level: Expert opinion

Metastatic disease is one of the main characteristics of advanced parathyroid cancer, and its presence significantly alters patient management and expectations. In parathyroid carcinoma,

although patients may achieve favourable long-term outcomes, metastatic disease influences disease-specific and overall survival. The routine use of radiation therapy, immunotherapy, or chemotherapy in the metastatic setting is not supported by any evidence. Once parathyroid carcinoma is metastatic, there is little chance of recovery; instead, most patients die from severe hypercalcaemia and/or other metabolic problems[23].

Because of the rarity of parathyroid carcinoma, it is difficult to determine the overall incidence of distant metastases[41]. Harari *et al.*[42,43] reported that one-third of patients develop metastases. As long as hypercalcaemia is managed at this point, prolonged survival remains feasible. The most common site of metastasis is the lung[44], followed by liver and bone[16]. There have also been reports of brain metastases[45–47]. Resection of metastatic lesions is advised when technically feasible[16,42,48]. This could involve performing craniotomies, hepatectomies, pulmonary resections, or bone resections. These metastasectomies are usually warranted for the reduction of severe hypercalcaemia associated with metastatic disease, even though curative treatment is unlikely. Resection of distant metastases has been demonstrated to increase patient survival in addition to having a temporary palliative effect. Severe hypercalcaemia, rather than a tumour mass effect, is the primary cause of death in patients with metastatic parathyroid carcinoma[49]. The aim of these resections is to eliminate remaining disease with distinct margins[48]. The best way to quickly control hyperparathyroidism and extend survival is to surgically remove metastases with radical intent, according to a systematic review and pooled analysis[50] of 79 patients with metastatic parathyroid carcinoma.

According to data from a study by Wei and Harari[43], up to 18 patients (58%) with recurrent or persistent disease had subsequent distant metastasis, which resulted in a lower 5-year overall survival rate of 34%, compared with 83% in those without distant metastasis. In contrast to a recent study by Asare *et al.*[27], who reported a metastasis rate of 23% and a 5-year overall survival rate of 16% in those with distant metastasis, an exceptionally high incidence of distant metastasis and superior overall survival were observed. Although the cohort of Wei and Harari had advanced disease, it is possible that aggressive reoperations prolonged the surveillance period by lowering the tumour burden and mitigating the consequences of hypercalcaemia-associated sequelae. This may have led to a greater likelihood of detectable structural lesions over the delayed course of the metastatic tumours.

Alternative techniques such as radiofrequency ablation have been employed in the management of lung metastases in patients with metastatic disease with unresectable disseminated lesions. Such treatment led to improvements in PTH and serum calcium levels[51,52]. Multiple liver metastases have been treated with a combination of transcatheter arterial embolization and radiofrequency ablation[53].

Preoperative evaluation and management

Statement 2: If parathyroid cancer is suspected on clinical and biological grounds, together with ultrasound imaging and sestamibi scintigraphy and/or single-photon emission CT (SPECT)/CT, contrast-enhanced CT and/or MRI to investigate local invasiveness, and 2-[^{18}F]fluoro-2-deoxy-D-glucose PET and/or choline PET and/or ^{99m}Tc sestamibi SPECT-CT to investigate functionality and presence of distant metastasis, should be preferred.
Consensus: Yes (94%)
Outliers: 6%
Evidence level: Low

As regards assessing the usefulness of imaging techniques in localizing parathyroid carcinoma before surgery, neck ultrasonography demonstrated 71% sensitivity and 100% specificity[42]. Infiltration of surrounding tissue and calcification both had a positive predictive value of 100% for malignant lesions in a retrospective analysis of ultrasound features in parathyroid tumours larger than 15 mm. Conversely, high negative predictive values were found for the absence of suspicious vascularity, thick capsule, and inhomogeneity[54].

Some 90 per cent of patients in a study by Villar-del-Moral *et al.*[55] had preoperative localization performed by ultrasonography, and 69% underwent sestamibi scintigraphy. CT was used in 31% of patients. Sestamibi scintigraphy was the most sensitive localization technique (95%) for identification of pathological glands, followed by ultrasound imaging (70%) and CT (68%). The most sensitive investigation for identifying cancerous signs was CT (21%), followed by ultrasound examination (19%), and sestamibi scintigraphy (5%).

Ultrasound imaging of the neck, CT, or MRI of the neck, chest, and abdomen are the primary methods used to identify distant or locoregional metastases. There is a dearth of information on nuclear medicine techniques in the metastatic context. Especially in patients with more aggressive and quickly evolving forms, total body imaging using ^{99m}Tc-labelled sestamibi and [^{18}F]FDG PET–CT may be a useful addition to conventional imaging in the initial staging[56,57]. Enhanced CT and MRI can provide valuable support for the diagnosis of metastases, but whether [^{18}F]FDG PET–CT, [^{18}F]FCH (fluorocholine) PET–CT, or [^{11}C]choline PET–CT should be used remains inconclusive[58]. SPECT–CT, four-dimensional (4D) CT, and ^{99m}Tc sestamibi imaging are additional imaging modalities that should be taken into account[4]. Combining imaging with ultrasonography, 4D CT, and sestamibi scintigraphy has 100% sensitivity for localizing parathyroid carcinoma, according to Christakis *et al.*[59]. According to one study[60], MRI can be used to identify metastases and recurrences, but there is currently insufficient evidence to support this.

Statement 3: There is no role for biopsy in patients with suspected parathyroid carcinoma
Consensus: Yes (92%)
Outliers: 4%
Evidence level: Low

Parathyroid cancer is usually identified only after surgery[39]. The diagnosis may be challenging, even for the experienced pathologist, and slides may even be shared with other national experts in case of any doubt, because observer-dependent bias in parathyroid neoplasm classification remains high. Unfortunately, parafibromin staining has not been widely adopted and histological features of parathyroid carcinoma can be seen in lesions that behave benignly. Parafibromin can enable the differentiation between atypical adenomas and carcinomas[61].

Fine-needle aspiration biopsy is not indicated for the diagnosis of parathyroid carcinomas as the diagnostic criteria are based on local invasion, not cellular characteristics. The histological definition of parathyroid carcinoma still needs one of the following findings, according the most recent WHO classification of parathyroid tumours[62]: angioinvasion (vascular invasion) characterized by tumour invading through a vessel wall and associated thrombus, or intravascular tumour cells admixed with thrombus; lymphatic invasion; perineural (intraneural) invasion; local malignant

invasion into adjacent anatomical structures; or histologically/cytologically documented metastatic disease. Documenting mitotic activity (for example mitoses per 10 mm^2) and the Ki-67 labelling index is advised for parathyroid carcinomas.

The risks of any biopsy for parathyroid carcinoma outweigh the potential benefits. This is because of concerns about rupturing the tumour capsule and raising the likelihood of tumour implantation, which could favour an incurable case of malignant parathyromatosis[2]. Moreover, for parathyroid carcinomas, fine-needle biopsy cannot be used to reliably differentiate between benign and malignant lesions, similar to the diagnostic difficulties of follicular thyroid cancer, for which the diagnosis requires capsular or vascular invasion[63]. Biopsying to diagnose primary hyperparathyroidism, and to exclude parathyroid carcinoma, is also not recommended by the American Association of Endocrine Surgeons guidelines[64].

Multidisciplinary team organization and patient information

Optimal advanced parathyroid cancer treatment goes way beyond the selection of an optimal surgical operation, leading to a disease-free neck. The need for evidence-based decisions requires the assembly of a multidisciplinary team (endocrine tumour board) to offer an individualized approach for each patient[65]. This team should consist of endocrinologists, endocrine/head and neck surgeons, nuclear medicine physicians, oncologists, radiotherapists, pathologists, and radiologists. It should be approved by the hospital and local authorities, and convene on a regular basis[66].

The patient should be monitored in the preoperative phase by members of the tumour board, who also have to assess all diagnostic tests, suggest the best course of treatment, and schedule follow-up depending on surgical findings, histology results, and patient preferences. Before scheduling any intervention, it is suggested that patients with advanced parathyroid cancer be referred to tertiary institutions that house endocrine tumour boards for evaluation.

Advanced parathyroid cancer is characterized by locoregional infiltration of vital structures such as the aerodigestive tract and/or distant metastases, and is thus accompanied by high rates of morbidity, worsening of quality of life, and a high risk of recurrence and mortality. After completion of the multidisciplinary team assessment, diagnostic processes, and preoperative evaluation, patients ought to be fully appraised of the potential complications, postoperative results, mortality risk, and disease-free survival rates.

Patient information to obtain informed consent should generally include the type and potential scope of the surgical procedure, the use of intraoperative adjuncts, the duration of hospital stay, the frequency of complications, and the likelihood of a repeat procedure or recurrence. Given that advanced parathyroid cancer can affect breathing, swallowing, and voice functions, it is important to explain the complications and extent of the associated surgical morbidity in detail.

Incorporating the possibility of attaining total locoregional disease clearance and the methods for verifying it after surgery ought to be a part of the patient consent procedure. It is also crucial to explain the overall survival rates, postoperative quality of life, and the need to adhere to follow-up protocols. To understand patients' perceptions after treatment, it is crucial to have direct and thorough conversations with them before surgery. Intraoperative decision-making should be discussed with patients during preoperative communication, particularly with regard to the management of the oesophagus, airway, and recurrent laryngeal nerve. Reviewing how different surgical choices affect function and oncological outcome is essential to ensure that the patient makes an informed decision.

Surgical treatment

Statement 4: *En bloc* resection, including the thyroid lobe and peritumoral/perithyroid tissue, avoiding capsular rupture, is recommended in patients with T1 parathyroid carcinoma.
Consensus: Yes (94%)
Outliers: 4%
Evidence level: Low

Surgery is still the standard treatment option for achieving control of locoregional disease in parathyroid cancer[64]. The best chance of recovery and an extended period of disease-free survival is provided by a high index of suspicion for this uncommon malignancy and sufficient *en bloc* excision of the tumour during initial surgery[67]. The goal of surgical resection should be to achieve negative margins, by means of an R0 resection, and also to control the endocrine derangements that affect morbidity and mortality[43]. Removal of the ipsilateral thyroid lobe and any adjacent structure may be needed to achieve this goal[68]. Using an open approach, the tumour should be excised with as little manipulation as possible to prevent capsule rupture and the spread of tumour cells throughout the surgical field[69,70].

En bloc excision consists of tumour resection, ipsilateral thyroid lobectomy and isthmectomy, tracheal skeletonization, and excision of any involved adjacent structures[71]. This has also been reported in a recently published systematic review[21] that included 3000 patients from 75 studies. On the other hand, Hu *et al.*[24] reported that *en bloc* resection was not related to improved disease-free or overall survival. The extent of surgery did not affect overall survival in patients with localized parathyroid carcinoma, according to a US National Cancer Database (NCDB) study[72] that included 555 patients. The study suggested that patients who are found to have parathyroid carcinoma, after undergoing local resection of the primary tumour only for a presumed benign indication, may be safely and closely monitored for recurrence, instead of undergoing immediate redo surgery. This study also examined the distinctions between radical surgery and local resection. Radical surgery included parathyroidectomy, ipsilateral thyroidectomy, central neck dissection, and, if necessary, lateral neck dissection. Local resection involved only parathyroidectomy. Before surgery, patients in the group undergoing radical surgery were more likely to know their lymph node status. Radiotherapy was administered to a high proportion of patients in both groups. Radical surgery did not significantly affect overall survival compared with local resection. Nevertheless, patients who underwent radical surgery as first intervention had an obvious preoperative or intraoperative indication of cancer and therefore suffered from more advanced disease with worse prognosis, leading to bias in the analysis.

Very recently, McInerney *et al.*[73] published a systematic review of management and outcomes. Only 7 of 3203 retrospective articles, concerning 2307 patients, were eligible. Throughout all studies, the most common surgical technique was parathyroidectomy alone, followed by *en bloc* resection with adjacent thyroid and/or nodal

tissue. There was no difference in postoperative morbidity, mortality, or survival between the surgical approaches. Those who underwent either type of surgery had longer overall survival than patients treated without operation. A different analysis[36], however, showed that there was overall 8% evidence of local recurrence following *en bloc* resection, as opposed to 51% after standard parathyroidectomy. Although only 27–39% of patients with localized parathyroid carcinoma receive *en bloc* resection with an accompanying central neck dissection of level VI lymph nodes, this has been advised for all patients in the absence of conclusive data[17,18,36]. According to a retrospective analysis[68] of one of the largest cohorts of patients from the NCDB diagnosed between 2004 and 2017, mortality was linked to both advanced age and the absence of surgical resection. Overall survival was not found to be associated with lymph node metastases, tumour size, or external beam radiation treatment. This is consistent with information provided by Asare *et al.*[27] in a previous NCDB data set cohort and Lee *et al.*[13] in a SEER database study. Radical *en bloc* resection seemed to have a marginally weaker correlation with survival in a study by Goldner and Fingeret[68]. Compared with patients who have less obvious intraoperative pathology, radical resection may be a confounding factor for more extensive disease at presentation, a finding that leads to more extensive surgical treatment. Wang *et al.*[74] reported that, among 234 patients, 60% had radical resection and these had a reduced recurrence rate compared with patients who just underwent parathyroidectomy.

Young *et al.*[75] compared the overall survival of patients who had parathyroidectomy alone, *en bloc* resection, or parathyroidectomy followed by delayed thyroid resection, and showed that patients who had more extensive surgery did not have a higher overall survival rate. Concurrent removal of nearby organs did not increase overall survival in a larger study[27] involving 733 patients with parathyroid carcinoma.

It is crucial to understand that frozen-section analyses cannot be used to differentiate between benign and malignant disease. Further resection to clear the margins is advised if the final histopathology report shows positive margins. Remarkably, the recurrent laryngeal nerve may be sacrificed during this subsequent resection, which may entail tracheal and oesophageal resection. In instances where invasion is not recorded, it is, however, unknown how hemithyroidectomy affects survival[42].

In patients without distant metastases, a reduction in hypercalcaemia is anticipated within 24 h after surgery. Full restoration of normal calcium levels may take 2–3 days[43]. Should the calcium level not drop after surgery, it is necessary to conduct additional diagnostic and therapeutic procedures as resection may have been incomplete[76]. Corrective surgery can be scheduled if the patient's serum calcium and PTH levels remain raised, the pathological picture demonstrates widespread invasion of the vascular, capsular, and/or perineural spaces, and the patient eventually remains symptomatic after precise preoperative imaging studies[69].

Statement 5: Centres with experienced endocrine surgeons that perform > 40 parathyroidectomies a year, dealing with locally advanced thyroid cancer, and that can provide both intraoperative and postoperative (adjuvant or palliative) support from other specialties should perform parathyroid cancer surgery.
Consensus: Yes (88%)
Outliers: 4%
Evidence level: Low

Performance data for a specific surgeon or an institution would have to be available to reliably answer this question. Experienced surgeons and surgical centres may provide a more appropriate level of surgery and adjuvant treatment, which could have an impact on patient outcomes.

According to Harari *et al.*[42], overall survival rates after 5 and 10 years were 78 and 67% respectively. Patients from various hospitals participated in this study, one of which was a tertiary referral centre for endocrine surgery. A lower death rate was observed when parathyroid carcinoma surgery was carried out in this centre as opposed to the other included hospitals. A reduction in mortality and complication rate was noted when the first surgery was performed in an academic tertiary-care endocrine surgery referral centre. It was recommended that individuals who may have parathyroid carcinoma should see a skilled parathyroid surgeon.

The best chance of recovery and improved results can be achieved by having the operation at a referral centre specialized in parathyroid surgery and neck resections[42,77]. The fact that parathyroid surgery is more likely to result in morbidity, failures, and the need for repeat procedures when carried out in low-volume settings has also been brought up in another consensus report from the ESES[78]. Consequently, high-volume settings (over 40 parathyroidectomies per year) should be the only places for challenging procedures.

Statement 6: A functioning recurrent laryngeal nerve with electromyographic (EMG) signals proximal to the infiltration site should be managed conservatively and disease clearance should be achieved while maintaining structural and, ideally, functional integrity of the nerve.
Consensus: No (31%)
Outliers: 33%
Evidence level: Low
Conclusion: A wide treatment corridor in regard to surgical decision-making for preserving or sacrificing a recurrent laryngeal nerve infiltrated by parathyroid carcinoma is proposed. In the event of entrapment of the recurrent laryngeal nerve—but preserved function as demonstrated via intraoperative neuromonitoring by EMG signals proximal to the infiltration site—the surgeon must decide between the mutually exclusive priorities of R0 resection on the one hand or preservation of nerve function on the other hand, which are both acceptable until newly emerging data show an advantage of one option. Those who voted 'disagree' argued that any infiltrated nerve should be resected to achieve R0 resection, otherwise trying to preserve the nerve may result in tumour rupture and seeding and impair the overall prognosis. Those who voted 'agree' argued that preserving the nerve should always be considered, even in R1 procedures.

The recurrent laryngeal nerve may be resected as part of the *en bloc* excision for parathyroid cancer because the nerve is vulnerable to tumour invasion and subsequent loss of function. Although it is rarely necessary, the extent of *en bloc* resection and tumour adherence may both require nerve sacrifice[79]. Resecting the nerve should be the decision if the parathyroid carcinoma is adherent to the recurrent laryngeal nerve. When possible, an immediate repair using an ansa cervicalis graft or an end-to-end anastomosis can be carried out[80]. Alternatively, unilateral atrophy of the vocal cord muscle can be compensated by postoperative functional training and augmentation of the paralysed vocal cord, for example by injection laryngoplasty[81].

Regardless of oncological outcomes, the management of recurrent laryngeal nerve infiltration certainly demands a high

level of surgical expertise in balancing preoperative and intraoperative options with local disease control and patient expectations, as complications related to voice and swallowing functions might prove permanent and debilitating.

Specific considerations

Lymph node involvement

Regional lymph node metastases may be present in patients with parathyroid carcinoma. The incidence of regional lymph node involvement at initial diagnosis varied greatly in the study of Schulte *et al.*[82], ranging from 6.5 to 32.1%. Meanwhile, there are conflicting results regarding nodal status[2,14,42,62]. For instance, Lo *et al.*[14] showed that positive lymph nodes were not linked to worse disease-specific survival. Accordingly, there is no proof that routinely dissecting the centrocervical compartment lymph nodes increases the survival rate. About 10% of patients may have central locoregional lymph node metastases[83]. As the central compartment has been involved in up to 10% of patients, and omitting central and/or ipsilateral jugular compartment dissection may carry a 1.5–2.0 times higher risk of both 5-year recurrence and death, central neck dissection has been proposed to be included in the initial surgical approach in all patients with parathyroid carcinoma[83]. Neck dissections have been described as one of the most complicated operations of the human body, requiring expert knowledge of regional anatomy and expertise gained by surgical experience in the neck area[84]. An increased risk of complications, such as recurrent laryngeal nerve injury and, particularly for the lateral neck, injury to various critical neurovascular structures and lymphatic leak, has been linked to surgical excision of bulky or extensive central and lateral neck disease[85].

The rate of cervical lymph node metastasis in 68 patients with parathyroid carcinoma was 19% at the time of initial surgery and 25% when reoperations for recurrences were included[86]. The presence of somatic or hereditary *CDC73* (parafibromin gene) mutations and high-risk Schulte staging are associated with the frequency of lymph node metastasis. For patients with high-risk factors, it has been recommended that central lymph node dissection be taken into account during corrective operations carried out following local resection of parathyroid carcinoma[86]. Remarkably, soft tissue infiltration in the lateral compartment was more common (58%) than lymph node involvement (32%) in the study by Wei *et al.*[79]. This was in excellent agreement with the review in a recent book chapter compiled by Pradhan *et al.*[87] (57% with soft tissue infiltration *versus* 32% with lymph node involvement). Positive lymph node status was not linked to disease-specific survival in a SEER cancer registry analysis[25], but malignant parathyroid tumours larger than 3 cm were linked to lymph node metastases. Patient risk of lymph node metastases may be categorized based on the size of the tumours.

Invasion of the trachea and/or oesophagus

Statement 7: In patients with limited (stage I or limited stage II according to Shin classification) involvement, tracheal shaving should be performed. In those with extensive (stage III or IV) involvement, tracheal resection and/or two-stage resectional surgery (following previous conservative surgery and adjuvant treatment) should be considered according to multidisciplinary team goals of care and patients' preferences.
Consensus: Yes (86%)
Outliers: 2%
Evidence level: Low

Statement 8: In patients with oesophageal involvement that does not extend into the lumen, only the involved musculature should be resected. When local disease control requires full-thickness excision and reconstruction, surgical options should be based on multidisciplinary team goals of care and patients' preferences.
Consensus: Yes (94%)
Outliers: None
Evidence level: Low

Invasion of adjacent structures such as the trachea or oesophagus by parathyroid carcinoma is very rare. The literature consists of very few case reports[88,89]. The management of tracheal invasion ought to involve local resection and repair, whereas the management of oesophageal invasion should entail resection of the muscularis layer[42,90]. Laryngopharyngo-oesophagectomy should be considered only in highly selected patients who are fully prepared for possible grave outcomes, according to Wei *et al.*[79].

Major vascular invasion

A shortened life expectancy can hardly be prevented in the event of severe vascular invasion, as distant metastases can form quickly as a result of haematogenous spread[23,79].

Medical treatment before surgery

The goal of medical management is to control the consequences of a raised plasma PTH level and consequent hypercalcaemia. As first-line treatment, intravenous fluids, diuretics, and bisphosphonates are used to lower the serum calcium concentration. Use of calcimimetic agents, such as cinacalcet, is advised if first-line therapy fails. Cinacalcet effectively reduces parathyroid carcinoma-induced hypercalcaemia by suppressing PTH secretion; however, more advanced tumours may not express the calcium-sensing receptor[21,91].

Does locoregionally advanced parathyroid carcinoma warrant four-gland exploration?

Statement 9: Locoregionally advanced parathyroid carcinoma does not require four-gland exploration in case it is sporadic. Familial cases may need bilateral exploration.
Consensus: Yes (86%)
Outliers: 6%
Evidence level: Low

There is no universal agreement on this, but research on all four glands may be necessary because multiple-gland carcinomas have been reported in the literature[92,93]. If parathyroid carcinoma is highly suspected during surgery, Kowalski *et al.*[77] suggested intraoperative inspection of all four parathyroid glands. Four-gland exploration combined with subtotal parathyroidectomy has been recommended in patients with concurrent renal hyperparathyroidism and parathyroid carcinoma[94].

Role of non-curative aggressive surgery

Statement 10: Cytoreductive surgery is of interest in terms of life expectancy. A non-R0 surgical resection can reduce hypercalcaemia and improve quality of life.
Consensus: Yes (80%)
Outliers: 20%
Evidence level: Low

Statement 11: When cytoreduction is believed not to be sufficient to reach adequate calcium and PTH level reduction, by evaluating patient condition and view, a multidisciplinary team decision should be taken.
Consensus: Yes (80%)
Outliers: 19%
Evidence level: Low

These considerations must be made to determine when surgery is not recommended for advanced parathyroid carcinoma: seeking a decision as a multidisciplinary team while considering the patient's condition, burden of invaded structures, patients in whom PTH and calcium reduction remain insufficient after cytoreduction was carried out, and patient decision.

Role of intraoperative adjuncts

Intraoperative parathyroid hormone measurement

The value of intraoperative PTH measurement in determining the resection of diseased glands is limited in parathyroid carcinoma, in contrast to parathyroid adenoma or multiglandular hyperplasia, where it is helpful during surgery. If available, it ought to be interpreted as a noteworthy decline in the value within the typical range, signifying disease clearance[35,48,95].

Hand-held radioguided γ probe

Use of a radioguided γ probe in the excision of recurrent parathyroid carcinoma has been described[96], even though its precise application and advantages in the surgical management of parathyroid carcinoma have not been thoroughly investigated. This particular modality can prove to be advantageous in accurately localizing recurrent parathyroid carcinomas[76].

Near-infrared autofluorescence

Near-infrared autofluorescence is a new diagnostic technique used to identify parathyroid glands. Compared with normal ones, hyperfunctioning parathyroid glands have heterogeneous and generally lower autofluorescence intensity[97]. Recent reports have documented the autofluorescence characteristics of parathyroid carcinoma[98]. As anticipated, cameras revealed no discernible near-infrared fluorescence in any of the tumours.

Intraoperative neuromonitoring

Statement 12: Regarding intraoperative adjuncts, nerve monitoring is recommended during advanced parathyroid carcinoma surgery.
Consensus: Yes (86%)
Outliers: 11%
Evidence level: Low

Because one of the most frequent complications of primary and revisional parathyroid surgery is recurrent laryngeal nerve injury, intraoperative nerve monitoring is beneficial for nerve dissection and functional prognostication in patients with expectations regarding vocal function[79].

Role of radiation therapy

Statement 13: Parathyroid carcinoma is known to be radioresistant and the impact of radiotherapy in the adjuvant setting is not known. The use of radiotherapy may be considered with a multidisciplinary team decision and may have value for palliative reasons.
Consensus: No (20%)
Outliers: 40%
Evidence level: Low
Conclusion: A wide treatment corridor in regard to the role of radiotherapy in advanced parathyroid carcinoma is proposed owing to the scarcity of evidence. Decisions by a multidisciplinary team in favour of or against radiotherapy for a patient are both considered acceptable until newly emerging data show an advantage of one treatment option. Those who voted 'disagree' argued that, because of the rarity of the disease, the impact of radiotherapy in the adjuvant and palliative setting is not known. It is also mentioned that parathyroid carcinoma is known to be radioresistant and there is lack of evidence regarding its radiosensitivity.

Because these neoplasms are usually radioresistant, there is currently insufficient evidence to support the use of radiation therapy as the main course of treatment. There is a lack of definite agreement on the use of radiation therapy in patients with parathyroid carcinoma, and no RCTs have been conducted. Although there is limited information available about other treatment options such as chemotherapy or immunotherapy, there is a dearth of data regarding the efficacy and appropriate timing of radiation therapy[43].

Only a small number of patients, particularly those with R1 resection, have undergone radiotherapy as an adjuvant treatment for parathyroid carcinoma[6,16,59,99–101]. Comparing overall survival rates of patients who received radiotherapy with rates among those who did not, retrospective data revealed no improvement. Except in patients having palliative care, the American Association of Endocrine Surgeons[64] opposes the use of external beam radiation. Whether radiation therapy should be used only late in the course of disease remains a matter of debate.

Postoperative radiation has been advised, however, by Munson *et al.*[102], Kirkby-Bott *et al.*[103], Selvan *et al.*[100], and Busaidy *et al.*[16], who support its use in lowering local recurrence rates. In patients with microscopic residual parathyroid carcinoma, Apaydın and Yavuz[104] recommended adjuvant radiotherapy to the neck to lower the risk of local recurrence.

Extensive resections in the initial surgical management are probably more important, according to a series[99] from a single centre that, although including only 11 patients, found no discernible effects of radiotherapy on survival. Furthermore, two national registry analyses[27,105] from the US NCDB independently demonstrated that there was no difference in overall survival rates between patients who received radiotherapy and those who did not. Genetic analysis appears to be a promising avenue for direct targeted therapies for patients with advanced parathyroid carcinoma in the future[106].

Recurrence and persistence of parathyroid carcinoma

As demonstrated in a genetic profiling study by Kutahyalioglu *et al.*[107], recurrent or persistent parathyroid carcinoma may also be classified as advanced parathyroid carcinoma. This is a highly aggressive disease, with recurrence rates ranging from 40

to 60%[2,13,108], and a median disease-free interval of 36 months after initial surgery[109]. However, reports of a longer interval of 15–20 years have also been published[110].

Multiple surgical interventions are frequently required owing to the high frequency of recurrence[3]. Reoperation is rarely curative, and recurrence is likely to develop eventually. Three to five times as many complications arise compared with the initial procedure[38,42]. The selected surgical approach was a significant predictor of death and recurrence in a cohort of 40 patients; the rate of recurrence decreased as the extent of operation increased[22].

When it comes to revisional surgery, Wei *et al.*[79] and Wächter *et al.*[111] reported that extended *en bloc* resection produced better results than other traditional surgical techniques, such as parathyroidectomy alone, for recurrent or persistent parathyroid carcinoma. A set of surgical techniques was used in accordance with their description of extended resection: dissection, usually from the lateral compartment towards the trachea, beginning from the normal tissue beyond the previous scar (the sample contained platysma muscle and prevertebral fascia); the trachea, oesophagus, common carotid artery, vagus nerve, and internal jugular vein were skeletonized; the surrounding thyroid and sternocleidomastoid muscle were removed to the extent indicated; the strap muscles could be sacrificed when necessary; where oesophageal infiltration was focal, the outer layer of the oesophageal muscle was resected, or limited resection of the full thickness of the oesophageal wall was carried out with direct repair; and laryngopharyngo-oesophagectomy and one-stage reconstruction of the oesophagus were used in patients with gross invasion of the cricoid cartilage and the entrance to the oesophagus. About the site of locoregional recurrence or persistence, upper aerodigestive tract invasion, and lateral neck soft tissue, paratracheal and paraoesophageal compartments were the most commonly involved sites, with rates of 58, 45, and 42% respectively. After this prolonged resection, the 5-year overall survival rate was 60%, as opposed to 17% following less drastic procedures, and the median expected survival time was improved to 90 months *versus* 13 months after local excision[79,111]. Therefore, in the absence of distant metastasis, extended *en bloc* resection may present a second opportunity for cure for patients with recurrent or persistent disease[21].

Villar-del-Moral *et al.*[55] used multivariable analysis and Cox regression models to detail predictors of tumour death and recurrence. Tumour recurrence was predicted by intraoperative tumour rupture, stage III Schulte classification, and the existence of mitotic features within parenchymal cells. Particularly for parathyroid carcinoma, intraoperative tumour rupture and distant recurrence were predictive of death. The study conducted by Tsai *et al.*[112] revealed that lack of bone metastasis, a disease-free interval of less than a year, and fewer than three operations were prognostic factors for recurrent disease.

Management of recurrent or persistent disease is challenging; it should be treated in centres with a high level of expertise in the field of neck endocrine surgery. The decision to reoperate should be made by a multidisciplinary team as patients with regional clinically evident disease are at high risk of disease persistence and new recurrence. At least two preoperative non-invasive imaging studies are required for tumour localization before surgical treatment of recurrences and/or metastases[38]. Although ^{99m}Tc sestamibi SPECT–CT is the recommended technique for identifying and evaluating cervical and extracervical lesions before the new surgery, its combined use with cervical ultrasonography is the most effective approach in the diagnosis of parathyroid carcinoma relapse[113]. As mentioned above, contrast-enhanced CT and/or MRI should be used to investigate local invasiveness, and [^{18}F]FDG PET and/or choline PET to investigate functionality and presence of distant metastasis. Before scheduling a remedial neck exploration, it is advised that at least two non-invasive studies looking for distant metastases be negative[67].

Prognosis

In general, parathyroid carcinoma has a good prognosis[28]. With 76–85% and 49–77% of patients alive at 5- and 10-year follow-up respectively, overall survival rates are better than those for most solid tumours[82]. The prognosis is affected by early diagnosis and the completeness of tumour resection[50,56]. Five-year overall survival ranges from 60 to 93%[15,16,25,75,79,106,114]. *En bloc* resection yields an 89% long-term survival rate and an 8% local recurrence rate, as opposed to approximately 51 and 53% respectively with initial incomplete surgery[36]. Even patients with incomplete tumour resection reported by Asare *et al.*[27] had longer overall survival than those who did not have surgery. The reason for this is unknown to the authors, but it is possible that resection reduces excessive PTH secretion and hence the morbidity associated with hypercalcaemia. This is also supported by the work of Zhou *et al.*[115], who showed that having surgery of any type improves survival compared with not undergoing surgery. If surgery is unsuccessful, these patients are, however, thought to have worse clinical outcomes, with a median disease-free period of no more than 2–3 years[22–24,42,74].

There is debate regarding the prognostic factors for parathyroid carcinoma. Numerous prognostic factors have been linked to mortality in previous research, such as tumour size[116], surgical outcomes[24,117], and the type of procedure used for primary and metastatic tumours[3]. Male sex, younger age, and higher calcium levels were considered unfavourable prognostic factors by Schulte *et al.*[6]. In a retrospective analysis[118] of 604 patients with parathyroid carcinoma in the SEER database from 2001 through 2018, age at diagnosis over 70 years, tumour size larger than 35 mm, and distant metastasis were independent risk factors for disease-specific mortality. Multivariable analysis of another data set of 609 patients with parathyroid carcinoma, extracted from the SEER, identified tumour size larger than 4 cm, age over 40 years, male sex, Caucasian race, distant spread, and poorly differentiated grade as independent risk factors for mortality[28]. In the largest study by Sadler *et al.*[119], positive surgical margins and positive lymph nodes conferred worse overall survival.

Rather than dying directly from the tumour burden, patients with parathyroid carcinoma typically die from metabolic complications of recurrent or persistent primary hyperparathyroidism[18,69,120,121].

Follow-up

Frequent monitoring is advised, which may involve biochemical monitoring of PTH and calcium homeostasis, neck ultrasonography, parathyroid imaging, and CT or MRI of the head, neck, and chest. Initially, depending on the severity of disease and the response to treatment, biochemical and radiographic monitoring is advised every 3–6 months. If there is a sustained remission, the interval may be extended to once a year[39]. The board of parathyroid cancer treatment[122] recommends checking patients every 3 months for the first 3 years, then every year for the next 5 years, and finally every year for the rest of their lives.

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Author contributions

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The authors declare no conflict of interest.

Data availability

Data are available on request to corresponding author.

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