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Review

Focus on Thyroid Cancer in Elderly Patients

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Abstract: Thyroid cancer is more aggressive in elderly patients due to biological causes related to age, histotype, and the advanced stage at diagnosis. In the elderly, both the diagnosis and treatment of thyroid cancer impact quality of life. This review aimed to collect and discuss the different therapeutic approaches in elderly patients affected by thyroid cancer. Our analysis examined the therapeutic surgical approach according to age and how this affects the prognosis of patients with thyroid cancer, along with how iodine 131 therapy is tolerated and how effective it is. Furthermore, we investigated whether levothyroxine suppressive therapy is always necessary and safe in elderly patients with thyroid cancer and the safety and efficacy of systemic therapy in the elderly. We also intended to identify peculiar features of thyroid cancer in elderly subjects and to evaluate how the disease and its treatment affect their quality of life.

Keywords: thyroid cancer; elderly; age

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1. Introduction

Thyroid cancer (TC) is the most common endocrine cancer; according to the latest global cancer data report, TC ranks 11th among malignancies [1]. Histologically, differentiated thyroid carcinoma (DTC) arises from follicular thyroid cells, and it is further subclassified into papillary thyroid carcinoma (PTC), the most common histological type; follicular thyroid carcinoma (FTC); and Hurthle cell carcinoma (HTC). Dedifferentiated thyroid cancer progresses from poorly differentiated thyroid cancer (PDTC) to anaplastic thyroid cancer (ATC). Medullary thyroid carcinoma (MTC) arises from neuroendocrine-derived parafollicular C cells [2]. The incidence of DTC increases with age as well as thyroid cancer recurrence [3–7]. Thyroid cancer is the only malignancy for which age is a prognostic marker in most staging systems [5,7,8]. The therapeutic management of DTC in elderly patients remains controversial [5]. The term "elderly" generally refers to the chronological age group of the population over 65 years of age [9]. The data available in the literature regarding the results in this age group are not numerous, and the incidence analysis as well as the prognosis in elderly patients are rarely reported [3,10–13]. The diagnosis of cancer as well as its treatment impact a person's quality of life (QoL). QoL and the acceptance of the disease are important in TC, since the follow-up is long thanks to good survival [14]. There are few studies in the literature that take into consideration the quality of life of patients with thyroid cancer [15–21]. The goal of this review was to investigate the peculiar features and treatment of DTC in elderly patients, including surgery, radioactive iodine 131 (RAI) therapy, hormone therapy, radiation, and targeted therapy, as well as the impact of thyroid cancer on QoL in this age group.

2. Materials and Methods

We carried out a search of the published literature without time limits using the following keywords: "thyroid cancer" and "elderly". Only English documents were included. Because they were outside of the main topic of this review, articles on the etiology and pathophysiology of thyroid cancer were excluded, while articles focusing on the treatment of thyroid cancer in the elderly were selected. The review was conducted according to the SANRA scale for the assessment of the quality of narrative review articles [22].

3. Thyroid Cancer in Elderly Patients

3.1. Peculiar Features of Thyroid Cancer in Elderly Patients

Some studies have reported data on peculiar features of thyroid cancer in elderly patients. In patients aged over 65 years, DTC presents itself at diagnosis with lymph node involvement [11,23–28], advanced-stage disease (III/IV) [11,23–25,27–30], distant metastases [11,23–25,27,28,30], multifocality [24,25], extracapsular extension [24–26,28], vascular invasion [11,26,29], and a low percentage of lymphocytic thyroiditis [29]. Regarding the histology, the follicular histotype [26], anaplastic carcinoma [27], and the undifferentiated form [11,30] are more frequent than in younger patients. Regarding these features, elderly patients have a significantly worse prognosis than younger subjects [30]; in addition, age has been identified as an independent risk factor for cancer-specific survival (CSS) [28]. Moreover, with increasing age, an increased risk of recurrence was observed together with a reduction in overall survival (OS) [26,27]. Factors that significantly increase the risk of recurrence in DTC patients >65 years old are the tumor size and lymph node metastasis (LNM) [4,31]. In a meta-analysis of 16 studies on thyroid cancer in the elderly, seven studies (7496 patients) contained data on the risk of recurrence after surgery, and the odds of recurrence increased 2.13 times (95% CI = 1.21, 3.75) [32]. Trimboli et al. showed that the median disease-free survival (DFS) was shorter in patients >55 years of age, and DFS decreased with advancing age. Furthermore, this group of patients had a significantly higher risk of recurrence than younger ones [33]. In DTC patients >60 years, cN1b, a tumor of size ≥4 cm, and extrathyroidal extension were significantly associated with the biochemical persistence of disease (BPD), and the age at surgery was associated with a thyroglobulin doubling time (Tg-DT) of <2 years independently of sex and staging [34]. In elderly patients with DTC, risk factors for CSS were male gender, African American ethnicity, tumors larger than 4 cm, extrathyroidal extension, and the presence of lymph node metastases and distant metastases [35]. The 120-month cause-specific survival rate of male and female patients undergoing surgery tended to gradually decline from age 60–64 years to ≥80 years [36]. In a retrospective study on 438 patients, a survival analysis identified factors associated with disease recurrence: primary tumor size >4 cm (hazard ratio (HR) = 2.49 (95% CI, 1.06–5.88), $p = 0.037$), lymph node metastases (HR = 2.59 (95% CI, 1.13–5.95), $p = 0.025$), and lung metastases (HR = 10.46 (95% CI, 3.50–31.33), $p < 0.001$). Patients who did not achieve remission after the first dose of RAI therapy had a higher risk of disease recurrence than those who did (HR = 2.02 (95% CI, 1.35–3.04), $p = 0.001$) [37]. An American study identified the categories of patients in which a difference in care was found in the diagnosis and treatment of DTC: these were elderly patients, socioeconomically disadvantaged patients, patients without medical insurance, patients coming from rural areas, and patients belonging to racial and ethnic minorities [38].

3.2. Surgery, Minimally Invasive Techniques (MIT), and Active Surveillance (AS)

It is known that elderly patients often have more comorbidities and higher rates of surgical complications, such as length of hospital stay, intensive care unit admission, and mortality [39–41]. For patients aged >80 years, surgical mortality can occur at a rate of up to 7% [42]. The characteristics of elderly patients, such as frailty, functional and cognitive limits, and malnutrition, as well as comorbidities and polypharmacological therapies, can

affect their ability to complete the therapeutic process and achieve full recovery after surgery [43]. Considering these aspects and the low proliferation rate of DTC, the surgical approaches in the elderly have been debated. The majority of the literature concerning the surgical treatment of thyroid cancer in the elderly consists of retrospective studies, lacking detailed information on the specific types of surgical treatment utilized. The studies distinguish between three different types of surgical intervention for thyroid cancer: near-thyroidectomy, thyroidectomy, and thyroidectomy with central and/or lateral nodal dissection. Additionally, comparing patients who were over 75 years of age with those who were under 75 years of age, no difference in the diagnosis of DTC or the type of surgery performed was found [27]. Overall postoperative morbidity was not significantly different between age groups [25], and no change in survival was observed between elderly patients treated with lobectomy and those treated with total thyroidectomy [30]. CSS was not different with respect to the type of surgery performed (lobectomy vs. total thyroidectomy) and with external beam radiation [35]. Patients > 85 years who underwent surgery had a better prognosis and overall cancer-specific survival ($p < 0.001$) than those who did not undergo surgery. For CSS, the 5-year survival and 10-year rates in surgically treated patients were 86.1% and 76.0%, while they were 47.9% and 44.9%, respectively, in unoperated patients [44]. In patients aged 65 or older, hospitalization days increased, with no significant change in surgical times or post-operative complications [45,46]. In patients > 70 years, there were no statistically significant differences in terms of post-surgical complications such as hypocalcemia and recurrent laryngeal nerve palsy (RLNP) compared to younger patients [24]. On the contrary, a study highlighted that RLNP was more common in the very elderly [46], and a meta-analysis confirmed the increased risk of complications (OR 1.82; 95% CI = 0.88–3.77) after thyroidectomy compared with younger patients [47]. Moreover, in elderly patients, the choice of the type of surgical procedure should be tailored considering the tumor and patient characteristics. No significant differences in outcomes between different types of surgery (lobectomy vs. total thyroidectomy) were found in patients with low-risk thyroid cancer, while total thyroidectomy increased the survival rate in high-risk thyroid cancer [28]. Comparing surgical times, complications, and hospitalization times between thyroidectomy and lobectomy, no statistically significant differences were observed, both resulting in safe operations in patients > 75 years old [7,48]. In patients aged > 66 years with DTC < 2 cm, short-term complications such as hoarseness, hypocalcemia, and hypoparathyroidism were observed in 20.4% of thyroidectomy patients compared to lobectomy patients, while the overall complication rates, including surgical wound infection or pneumonia, were not different between the two types of surgery. In a multivariate analysis, short-term complications were independently associated with total thyroidectomy (OR = 1.99), comorbidity index > 2 (OR = 1.43), female gender (OR = 1.34), and black versus white (OR = 1.65; all $p < 0.01$) [36]. Thyroidectomy + lymphectomy in elderly subjects (>75 years) showed a statistically significant difference in terms of transient hypoparathyroidism and temporary unilateral recurrent nerve damage, with higher incidence in elderly subjects compared to thyroidectomy alone [49]. The indication for the surgical approach varies considerably for different types of thyroid cancer; in fact, some patients with low-risk papillary thyroid microcarcinoma (PTMC) may opt for active surveillance (AS) rather than immediate surgery [50–52]. The indication for AS could be considered in adult patients with low-risk PTMC without lymph node metastases, vocal cord paralysis, or extrathyroidal extension (ETE) present at diagnosis [53]. Supporting these indications, an analysis of the Surveillance, Epidemiology, and End Results (SEER) data of patients with DTC aged > 66 years with clinical stage T1N0M0 showed that the surgical treatment and, when indicated, RAI therapy did not affect CSS ($p > 0.05$) [32]. A multivariate logistic regression analysis of PTMC patients aged > 55 years showed that multiple tumor foci, extrathyroid extension, and an irregular morphology of thyroid nodules were independent risk factors for central LNM of PTMC ($p < 0.05$). For this reason, active surveillance should be proposed in selected cases of elderly subjects with low-risk PTMC [54]. In patients > 70 years of age, surgery for DTC > 1 cm led to an 85% 10-year OS,

whereas, in patients in whom surgery was contraindicated due to age, medical condition, high surgical risk, or the risk of complications due to comorbidities, a 10-year OS of 62.6% was found. In untreated microcarcinoma patients, none died of a specific cause or disease progression [55]. In low-risk DTCs, elderly patients (>75 years) had significantly worse 5-year cumulative survival than younger patients, and the 2-year cumulative survival rate of elderly patients with high-risk DTCs was significantly lower in patients under active surveillance than those treated surgically [56]. Lohia et al. created a competitive risk model to identify the cumulative incidence of mortality from other causes, to define groups of patients with a life expectancy of less than 10 and 15 years. According to the authors, in patients with a low recurrence risk (T1a), with a life expectancy of less than 10 years (any patient aged > 80 years with CCS ≥ 1, as well as any patient > 70 years with CCS ≥ 3) and patients with a life expectancy less than 15 years (any patient > 80 years regardless of Charlson comorbidity score (CCS ≥ 0), as well as patients > 70 years with CCS ≥ 1), active surveillance should be considered [57,58]. If the surgical option is necessary for an appropriately selected patient with a limited life expectancy, de-escalation from total thyroidectomy to lobectomy is advisable [57]. After the publication of the 2015 ATA guidelines, elderly (>65 years) and super-elderly (>80 years) patients were more likely than younger patients (<65 years) to undergo lobectomy (aOR = 1.1, 95% CI: 1.03–1.2, $p = 0.002$, and aOR = 1.5, 95% CI: 1.3–1.7, $p < 0.001$) and active surveillance (aOR = 1.5, 95 CI %: 1.4–1.7, $p < 0.001$, and aOR = 6.5, 95% CI: 5.4–7.7, $p < 0.001$) versus total thyroidectomy surgery [38]. The adoption of AS should take into consideration not only the tumor characteristics but also the patient psychological profiles and medical team expertise [59]. Minimally invasive techniques (MIT) are an alternative to surgery in patients with thyroid disease, with similar efficacy, fewer complications, and better quality of life and aesthetic results compared to surgery. They could be an alternative in elderly patients who present severe comorbidities or are ineligible for surgery, and others who refuse invasive surgery [60]. MIT for malignant thyroid disease management include ethanol ablation (EA) [61–63], laser ablation (LA) [64,65], radiofrequency ablation (RFA) [31,66,67], microwave ablation (MWA) [68,69], cryoablation, and High-Intensity Focused Ultrasound Ablation (HIFU) [70]. The choice of treatment modality is based on the specific competences and resources at the individual center considering MIT, preferentially in the context of a multimodality approach, in patients with low-risk PTMC and other primary thyroid cancers. MIT for DTC may have indications for cervical recurrence, a previous surgical neck dissection, the presence of surgical complications, small-sized metastases, and limited latero-cervical lymph node involvement [61]. A systematic review and meta-analysis demonstrated that thermal ablation was an excellent local tumor control method in patients with low-risk PTMC, with low major complication rates at 5 years, but the data referred to the young population [71]. The existing literature is ambivalent concerning the significance of patient age upon surgical versus nonsurgical treatment outcomes for low-risk thyroid cancer; for this reason, surgery, MIT, or active surveillance can be taken into consideration in the elderly from the perspective of precision medicine, in the context of the disease management team (DMT), for thyroid cancer.

3.3. Hormone Replacement Therapy

Suppressive therapy with thyroxine is used both as a replacement for thyroid gland function and as a treatment to inhibit thyroid-stimulating hormone (TSH) secretion by the pituitary gland, to prevent thyroid tumor recurrence or metastasis [72]. Levothyroxine suppressive therapy is independently associated with longer OS in high-risk patients, and a semi-suppressive thyroid hormone therapy led to an improvement in OS in stage II patients [73]. Compared to young subjects, a 20–30% lower levothyroxine dose is required in the elderly to achieve TSH suppression [74]. Older people, especially those >80 years, have a reduced rate of peripheral degradation of thyroxine, which is associated with an increase in negative feedback exerted by thyroxine at the pituitary level, leading to a de-

crease in TSH secretion. For this, despite the slight reduction in the absorption of levothyroxine due to the increased central feedback, lower doses of levothyroxine are required [74]. Elderly subjects may have comorbidities that make it necessary to take multiple drugs, such as phenytoin, propranolol, cholestyramine, ferrous sulfate, and warfarin [75], which may interfere with the absorption and/or metabolism of levothyroxine. For this reason, it is important to monitor the TSH value together with the free fractions at the beginning of the therapy and during the follow-up. One cause of failure to achieve the therapeutic target of TSH may be the patient's poor compliance with the correct intake of levothyroxine [76]. Follow-up data obtained 5 years after surgery showed significant differences in the occurrence of arrhythmia, insomnia, and anxiety among several groups stratified according to TSH serum values (patients at 0.1–0.3 mIU/m and <0.1 mIU/mL compared to those at 0.3–0.5 mIU/mL) but there were no differences in recurrence and metastasis [77]. The bone loss and cardiac toxicity caused by thyrotoxicosis are known from the literature; therefore, it is highly recommended to monitor cardiac function and bone density in elderly patients on suppressive treatment with levothyroxine [73]. In the Framingham Heart Study, patients older than 60 years with values of TSH ≤ 0.1 mIU/L had an adjusted relative risk of 3.8 for the development of atrial fibrillation during a 10-year follow-up, and those with TSH values between 0.1 and 0.4 mIU/L had an adjusted relative risk of 1.6 [78]. In conclusion, the beneficial effect of TSH suppression in reducing the recurrence rates of DTC should be evaluated for potential complications in the elderly.

3.4. Radioactive Iodine I-131 (RAI) Therapy

RAI therapy in thyroid cancer can be considered in an adjuvant or therapeutic setting. Age has been suggested to be related to the low prevalence of RAI avidity [79,80]. However, a survival benefit can only be expected for patients with RAI-avid lesions [81–83]. During the therapy, a period of isolation is required to limit radiation exposure after the administration of radioactive iodine to people other than the patient (according to local regulations). During isolation, patients must follow the instructions of the staff to limit exposure and maintain self-care in eating, dressing, and going to the bathroom [82]. RAI therapy in elderly patients with significant cognitive impairment or dependent patients may not be feasible. Because of this, brief contact with relatives to assist patients may be permitted in some cases after obtaining informed consent, according to local guidelines [84]. RAI therapy is usually very well tolerated. Short-term adverse effects are rare but include nausea, abdominal discomfort, salivary dryness, and dry eyes [85]. Over time, xerophthalmia and xerostomia tend to be the most problematic [85,86]. Serious but rare complications include bone marrow suppression and radiation pneumonitis. The development of second tumors several years later in patients with thyroid cancer treated with RAI therapy is reported in the literature [87]. The risk of adverse effects varies depending on the dose administered and accumulation caused by repeated RAI treatments [84]. Stimulation of TSH is required for the absorption and organification of radioactive iodine [88], which is obtained with the withdrawal of levothyroxine to achieve biochemically and clinically hypothyroid patients, with significant negative effects on quality of life [89,90]. In elderly patients, hypothyroidism, in addition to the classic symptoms, leads to several risks that must be monitored for potential cardiac effects (worsening of heart failure and water retention and angina/cardiac ischemia) [74]. A severe state of hypothyroidism is associated with reversible conditions of renal insufficiency [91], which may decrease radioactive iodine clearance and increase bodily exposure. Further deterioration may occur in patients with memory impairment [74]. The use of recombinant human TSH (rh-TSH) avoids the need to send the patient into hypothyroidism [92], simulating the hypothyroid state [93,94]. The use of rh-TSH may reduce the blood total body radiation dose through increased renal clearance in euthyroidism [95]; this is especially important in elderly patients, in whom renal failure may be a comorbidity. The empirical dosing strategy (150–200 mCi) often results in administered RAI activity exceeding the maximum tolerable activity (MTA), with a safety limit of 200 cGy (rads), in the blood or bone marrow in many

patients with metastatic thyroid cancer. Empirical doses of 140 mCi exceed the MTA in 13% of patients aged 80 years and older at the time of dosimetry. However, an empirical dose of 200 mCi would exceed the MTA in 8–15% of patients < 70 years of age, 22% of patients 70–79 years of age, and 38% of patients ≥ 70 years of age at 80 years old, while an empirical dose of 250 mCi would exceed the MTA in 50% of patients 70 years of age or older at the time of dosimetry. Doses greater than 150 to 200 mCi often expose the bone marrow to more than 200 cGy of radiation in older patients. Dosimetric studies should be performed before administering more than 200 mCi to patients over 70 years of age with radioiodine-avid metastatic disease [96]. In the classic variant of papillary carcinoma (cPTC), the prevalence of RAI absorption concerning age was 41.5% for patients younger than 55 years, but this decreased significantly to 8.1% for those aged 55 or older, while the overall prevalence of uptake was 80.1% in follicular carcinoma (FTC), without a correlation with age [81]. One hypothesis for the possible reduced uptake appears to be the reduced expression of the sodium iodide symporter (NIS), which is also observed in the elderly or those with large-diameter tumors [97]. Female patients > 70 years of age undergoing one treatment (74%), two treatments (18%), three treatments (5%), and four treatments (3%), with median RAI activity of 150 mCi on rhTSH or withdrawal thyroid hormone (THW), showed, at 0–3 months after radioiodine therapy, a statistically significant decrease in platelets, white blood cells (WBC), and hemoglobin (Hb). The mean platelets, white blood cells, and hemoglobin in women, as well as lymphocytes, remained low (but within the reference range) one year after treatment. Platelet suppression was present with activity > 100 mCi and WBC and Hb suppression only with activity > 150 [98]. Empirical RAI therapy in elderly patients resulted in mild bone marrow suppression, with little clinical significance and with no clinically significant cytopenic events during follow-up [98]. RAI therapy in the adjuvant setting and for distant metastases in patients aged > 65 years showed that after an oral 131I dose with standard activity 150–200 mCi, 56.14% had 131I avid lesions, while 43.86% showed no therapeutic concentration of 131I [99]. In conclusion, a lower prevalence of RAI avidity has been linked to age, and the withdrawal of hormone replacement therapy in the elderly population can potentially cause cardiac effects and renal insufficiency. To prevent hypothyroidism, rh-TSH is preferred. Additionally, administering doses greater than 150 to 200 mCi often results in the bone marrow being exposed to more than 200 cGy of radiation, which is why dosimetric studies are recommended for patients over 70 years old.

3.5. External Beam Radiotherapy (EBRT)

Data on EBRT in the context of thyroid cancer in the elderly are scarce. From the available literature, it appears that radiation therapy in the neck region can be helpful as a supplementary treatment for patients above the age of 40 with inoperable large tumors or for those with remaining or recurring disease. This is particularly true when the tumor is unable to absorb radioactive iodine [35,75]. EBRT in the general population, not only in the elderly, may play a role in the treatment of DTC, either as an adjuvant therapy in selected cases or as an adjunctive therapy in patients with persistent or metastatic symptomatic disease, considering the toxicity. EBRT is often used for the treatment of patients with bone metastases and related symptoms [100]. The toxicity related to radiotherapy of the neck is divided into acute (in conjunction with treatment) and late (persistent). The most common acute complications are mucositis, skin erythema, desquamation associated with pain, weight loss, and the need for pain relief therapy with opioids, as well as hospitalization and sometimes tube feeding. Other types of acute toxicity include xerostomia, hoarseness, and taste perversion [101]. Late complications are less common and include esophageal stricture and chronic dysphagia ranging from nasogastric sores for feeding to tracheostomy placement for laryngeal stricture or edema [102]. Newer radiation techniques, compared to conventional radiation therapy, reduce the risk of late complications because they allow the precise targeting of the thyroid bed, with less radiation applied at adjacent critical structures such as the esophagus, trachea, and larynx [84]. In conclusion,

the use of EBRT in the elderly is reliant on experience in other patient settings, given that there are no data in the literature.

3.6. Target Therapy

The definition of radioiodine refractory DTC (RR-DTC) according to the 2015 ATA guidelines is as follows: (1) the primary and/or metastatic lesions do not absorb 131I out of 131I-WBS; (2) the primary and/or metastatic lesions do not demonstrate the ability to concentrate 131I, whereas, before, they were avid for 131I; (3) 131I is concentrated differently in some lesions at the 131I-WBS but not in others; and (4) primary and/or metastatic lesions show progressive disease (PD) within 1 year of 131I treatment despite sustained 131I concentrations [50]. Conventional chemotherapy is not associated with lasting responses, while it has significant toxicity [103]. Tyrosine kinase inhibitors (TKIs) have been shown to be a treatment for thyroid cancer patients with metastatic or locally advanced RR-DTC. TKIs are administered orally and their mechanism of action is by blocking the tyrosine kinase receptor at various levels (VEGFR 1–3, FGFR 1–4, PDGFR-alpha, RET, and KIT), thereby inhibiting the proliferation signal [104]. Evidence has shown that TKIs lead to an antitumor response even at lower than optimal dosages; therefore, patients continue treatment at the lowest tolerated doses [105,106]. In consideration of comorbidities and polypharmacological therapies in the elderly, it must be kept in mind that that TKIs are metabolized via cytochromeP450 system 3A4 [107]. Drug inhibitors of this cytochrome include common drugs such as amiodarone and verapamil, and antibiotics such as macrolides and azole antifungals. Enzyme inducers include dexamethasone, rifampicin, St. John's wort (herbal remedy for depression), and pioglitazone. In Italy, the two TKIs approved and reimbursed by the National Health System for the treatment of DTC are lenvatinib (first line) and cabozantinib (second and/or third line). In the SELECT study, lenvatinib led to a significantly longer median progression-free survival (PFS) of 18.3 months, compared to 3.6 months in the placebo group, for patients in the treatment arm [108]. A subgroup analysis of PFS observed that patients < 65 years had a slightly more favorable outcome of 20.2 months compared with 16.7 months in patients > 65 years. AEs were reported in 97.3%, with 75.9% of patients experiencing a grade 3 or more serious adverse event, and 14% of patients needed to discontinue treatment due to side effects [100]. Two of the most common AEs were hypertension and proteinuria [109]. In a sub-analysis of the SELECT study dividing patients by age (<56 years and >71 years), no significant difference in PFS was observed between the two groups in terms of the safety and efficacy of lenvatinib treatment. The incidence of AEs (grade ≥ 3) was significantly higher in older patients than in younger patients (89% vs. 67%, respectively) [110]. Elderly patients also required treatment dose reductions when AEs occurred, with the first reduction being early. In the elderly population, a higher prevalence of hypertension and proteinuria has been observed, as well as diarrhea, which easily leads to dehydration in the elderly [100]. The phase 3 COSMIC-311 study evaluated cabozantinib versus a placebo in patients with RR-DTC who previously had been treated with sorafenib and/or lenvatinib. Brose et al. demonstrated that cabozantinib was able to increase progression-free survival compared with a placebo (11.0 months, 96% CI: 7.4–13.8, vs. 1.9 months, 96% CI: 1.9–3.7, $p < 0.0001$) and ORR (11.0%, 96% CI: 6.9–16.9% vs. 0%, 95% CI: 0.0–4.1%, $p = 0.0003$). One complete response was observed in the cabozantinib-treated group. The subgroup analysis confirmed the efficacy in elderly patients (over 65 years), also showing a response in all the evaluated subgroups: size, metastatic site, previous therapy, and DTC histology. Severe AEs occurred in 62% of the patients treated with cabozantinib. Hypertension (12%), erythrodysesthesia (10%), and fatigue (9%) were the most common AEs [111], but no data are available regarding the incidence and grade of AEs in the elderly. In the phase III DECISION trial, sorafenib demonstrated a significant increase in PFS in patients with RR-DTC [112], but there are no data in the literature for elderly patients. Two novel selective RET inhibitors with efficacy in advanced RET-altered cancers have been developed, selpercatinib and pralsetinib. Both selpercatinib and pralsetinib have received approval for

the treatment of selected adults with locally advanced or metastatic RET fusion-positive thyroid cancer requiring systemic therapy following prior treatment with sorafenib, lenvatinib, and/or cabozantinib, but there are no data on the elderly population [113–115]. Larotrectinib, a potent and highly selective small-molecule inhibitor of all three tropomyosin kinase (TRK) receptor proteins, was developed for patients of any age and with any type of cancer (an age- and tumor-agnostic therapy), but there are no data on the elderly [116]. In conclusion, the literature data on lenvatinib and cabozantinib demonstrate their safety and efficacy in the elderly, while data are not available on selpercatinib and larotrectinib in this age setting.

3.7. Quality of Life

DTC in the majority of cases has a very good prognosis, with an overall long-term survival rate of more than 90%. At present, it is known that the diagnosis and cancer management impact various aspects of a patient's quality of life (QoL), and monitoring these changes is critical. In addition to mortality, cancer can cause significant morbidity, not only from the disease but also from the treatment. This is especially true for DTC patients, who mostly have a long survival period. The Short-Form Health Survey 36 (SF-36) is a generic QoL tool; it is divided into 36 questions that can be self-administered to estimate a health profile that includes eight domains. QoL analysis was severely impaired in 67% and 6% of unoperated and operated patients > 75 years old, respectively, suggesting that surgery for DTC increases the survival rate and promotes the quality of life of patients [56]. Physical functioning was worse in thyroid cancer survivors aged ≥ 50 and those with a lower educational level, who needed more follow-up attention [15]. When comparing the quality of life test results between thyroid cancer survivors and age- and sex-matched controls, thyroid cancer survivors were observed to more often have >2 comorbid conditions and lower educational levels. No differences were found between elderly thyroid cancer survivors and an elderly normative sample on the EORTC-QLQ-C30 functioning scales [16,117,118]. Mols et al. found that adolescent and young adult thyroid cancer survivors reported statistically and clinically significantly worse physical, role, cognitive, and social functioning and more fatigue and financial problems than the normative sample [16]. It seems that younger thyroid cancer survivors are more affected than older survivors. Additionally, the lower HR-QoL in older survivors is likely due to their age, not cancer [16]. The analysis of two questionnaires, The World Health Organization Quality of Life Brief Version (WHO QoL-BREF) and Acceptance of Illness (AIS), by Juzwiszyn et al. in patients undergoing thyroidectomy highlighted the significant worsening of QoL after thyroidectomy, both in the physical and psychological fields. Quality of life in all domains was significantly worse in the elderly. As regards the elderly, both before and after surgery, worse acceptance of the disease was observed [17]. In the Japanese population, using a mixed-methods design of surveys and semi-structured interviews in patients with an average age of 64 years, Davies et al. highlighted that concern about cancer was common among thyroid cancer patients under active surveillance, which was comparable to concern among actively treated patients. Levels of concern about cancer reported by patients under active surveillance decreased over time, and patients expressed satisfaction with the decisions made during disease management [119]. PTMC patients who underwent surgery had more complaints and were more anxious and depressed than the AS group (THYCA-QoL and HADS questionnaire scores) in patients < 60 years old, with all scales comparable between those who underwent total thyroidectomy and those who underwent lobectomy. These results suggest that AS should be taken into consideration with regard to the patient's QoL and personality [120]. The choice of the type of treatment can affect the QoL of patients affected by PTMC. Better psychological health was observed in the AS group compared with surgery, both at baseline and during follow-up [121]. Physicians' approach and communication can influence the treatment strategy and patients' decisions, especially in patients at low risk, and psychological support should be offered

to patients during the diagnostic and therapeutic work-up [122]. The impact of the therapeutic choice, both surgery or MIT and active surveillance, has an impact on the patient's quality of life, which must be considered together with the characteristics of the tumor to personalize the treatment.

4. Conclusions

More aggressive forms of DTC occur often in the elderly, presenting with larger tumors, local extension, and/or distant metastases at diagnosis. Survival rates decline with advancing age, regardless of the degree of differentiation of thyroid cancer. The main negative prognostic factors in elderly patients with DTC are more aggressive histological types, the presence of comorbidities and disabilities, and often a delayed diagnosis (Table 1).

The existing literature is ambivalent concerning the significance of patient age in terms of surgical versus nonsurgical treatment outcomes for low-risk thyroid cancer; for this reason, surgery, MIT, or active surveillance can be taken into consideration in the elderly.

Compared to young subjects, a 20–30% lower levothyroxine dose is required in the elderly to achieve TSH suppression, and attention may be paid to bone loss and cardiac toxicity.

RAI therapy in the elderly is often administrated with rhTSH to avoid the complications of hypothyroidism. In the elderly, reduced iodine uptake by the lesions can be observed, and it seems that this depends on the reduced expression of the sodium iodide symporter (NIS), which is also observed in the elderly or in large-diameter tumors.

EBRT must be taken into consideration regarding the patient and the malignancy's characteristics, as the therapeutic benefits may not always outweigh the risk, especially in elderly patients.

In elderly patients becoming metastatic with RR-DTC-resistant disease, tyrosine kinase inhibitors such as lenvatinib and cabozantinib led to longer median progression-free survival. New target therapies such as selpercatinib/pralsetinib or larotrectinib are age- and tumor-agnostic therapies with a good safety and efficacy profile.

As regards the elderly, in addition to cancer and its treatment, a major factor that affects the quality of life is advanced age; therefore, attention must be paid to this age group, in terms of both diagnosis and disease treatment.

Table 1. Key points in the treatment of thyroid cancer in the elderly.

	Thyroid Cancer in the Elderly
Peculiar features DTC	More frequent lymph node involvement, advanced stage disease (III/IV), distant metastases, multifocality, extracapsular extension, vascular invasion, follicular histotype, anaplastic carcinoma, and undifferentiated form.
Surgery	The benefit of surgical intervention in high-risk thyroid cancer is demonstrated. In low-risk thyroid cancer, lobectomy can be considered. Increased days of hospitalization, contrasting data on the increased surgery complications.
MIT, AS	In low-risk thyroid cancer (T < 1 cm, without lymph node metastases, vocal cord paralysis, or extrathyroidal extension) or high surgical risk, MIT or AS can be taken into consideration in the elderly.
Hormone replacement therapy	When necessary, suppressive treatment with levothyroxine can be proposed in the elderly, monitoring cardiac function and bone density. Preference for semi-suppressive treatment in low- and intermediate-risk and selected cases of high-risk thyroid cancer.

RAI therapy	Dosimetric studies should be performed before administering more than 200 mCi to patients over 70 years of age.
EBRT	No data are available in elderly; clinical indications are derived from other patients' age.
Target therapies	TKIs lenvatinib and cabozantinib are safe and effective in elderly. New tumor-agnostic therapies are available but there are no data on the elderly.
Quality of life	Better psychological health at baseline and physical and psychological health at follow-up in the AS than in the surgery group. No differences in QoL were found between elderly thyroid cancer survivors and an elderly normative sample.

DTC: differentiated thyroid cancer, MIT: minimally invasive techniques, AS: active surveillance, RAI therapy: Radioactive Iodine 131 Therapy EBRT: external beam radiotherapy, QoL: quality of life.

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