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ISSN 2168-5452 (Print)  ISSN 2168-5460 (Online)
https://www.scirp.org/journal/ijohns

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International Journal of Otolaryngology and Head & Neck Surgery (IJOHNS)

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A Case of Secretory Carcinoma That Occurred in the Buccal Submucosa

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Abstract
Secretory carcinoma (SC) is a malignant salivary gland tumor that has been first reported by Skalova et al. in 2010. Histologically, it shows solidly infiltrated with very small cystic cavities and cribriform and papillary features and includes periodic acid-Schiff stain-positive, acid-fast secretions. The cells have oval nuclei, and vacuolated cytoplasm and foamy secretions are seen. Anaplasia is not strong and mitotic figures are rarely seen. These features closely resemble AciCC. Immunohistologically, it is thought to be positive for S-100 protein, vimentin, and mammaglobin and negative for DOG1. The presence of the ETV6-NTRK3 fusion gene is essential in diagnosing secretory carcinoma. In this report, we describe a case of SC in a 52-year-old woman. She was referred to our center because of a mass in left buccal mucosa. A soft and elastic submucosal mass measuring approximately 10 mm × 10 mm in size with a smooth surface was seen in the buccal mucosa in an area corresponding to the left mandibular canine to premolars. The imaging findings revealed that a high-intensity lesion was seen on T2-weighted images. Immunohistochemical staining for S-100 protein and vimentin were positive. Furthermore, genetic examination detected the presence of the ETV6-NTRK3 fusion gene. Based on these findings, the definitive diagnosis was secretory carcinoma.

Keywords
Secretory Carcinoma, ETV6-NTRK3 Fusion Gene, Buccal Mucosa

1. Introduction
Mammary analogue secretory carcinoma (MASC) is a malignant salivary gland...
tumor that was first reported by Skalova et al. [1] in 2010. Histopathologically, it features a histological image reminiscent of secretory carcinoma of the breast, while also harboring the ETV6-NTRK3 fusion gene. Because there were previous patients with the ETV6-NTRK3 fusion gene among tumors classified as a subtype of acinic cell carcinoma (AcCC), it came to be labeled as secretory carcinoma in the 2017 World Health Organization (WHO) classification. As it has been a recently established disease entity, there are few reports. Moreover, secretory carcinomas are thought to occur mostly in the parotid gland in previous reports; occurrence in the minor salivary glands is considered to be rare [2]. We herein report a case of secretory carcinoma that occurred in the buccal submucosa, together with a discussion of the literature.

2. Case

A 52-year-old woman had felt a mass in her left buccal mucosa since 3 months. However, she took no action as there was no pain. When receiving dental treatment by her general dental practitioner, she was told it was a lesion and was referred to our center. She had a history of uterine myoma, hyperlipidemia, and diabetes (hemoglobin A1c 6.5%). A soft and elastic submucosal mass measuring approximately 10 mm × 10 mm in size with a smooth surface was seen in the buccal mucosa in an area corresponding to the left mandibular canine to premolars (Figure 1). The mass had poor mobility and no tenderness was noted. Yellow lipoma-like lesions were seen in the anterior and posterior portions of the mass. Enlarged lymph nodes were palpated in the right submandibular region. Delineation of the lesion from computed tomography (CT) findings was difficult due to metallic artifacts, but an enlarged lymph node measuring 15 mm × 10 mm in size was seen in the left submandibular region. In magnetic resonance imaging (MRI) findings, a high-intensity lesion measuring 10 mm × 9.5 mm × 6 mm in size was seen in the left buccal region on T2-weighted images (Figure 2). No obvious capsular structure was seen, the deep portion was in

![Figure 1. Oral findings. A soft, elastic submucosal mass measuring approximately 10 mm × 10 mm in size with a smooth surface is seen in the buccal mucosa in an area corresponding to the left mandibular canine to premolars (arrow). Yellow lipoma-like lesions are seen in the anterior and posterior portions of the mass (arrowhead).]
Figure 2. MRI findings. A high-intensity lesion measuring 10 mm × 9.5 mm × 6 mm in size is seen in the left buccal region on T2-weighted images (arrow).

contact with the buccinator, and the border was rather indistinct. Thus, invasion was a possibility and the findings were suggestive of a minor salivary gland malignancy. Clinically, it was diagnosed as a left buccal submucosal salivary gland malignancy.

3. Treatment and Course

Following fine needle aspiration biopsy of the enlarged lymph node in the left submandibular region, the tumor was diagnosed as Class II. Clinically, however, metastasis could not be excluded and we proposed resection of the left buccal submucosal malignancy and neck dissection. However, the patient refused consent for the neck dissection. Therefore, with the promise of rigorous postoperative follow-up, resection of the left buccal mucosal malignancy was performed under general anesthesia in October 2016. The resection was performed along with a sufficient margin of safety around the tumor, including the lipoma-like lesions. The tumor was resected, and after partial plication anteroposteriorly the low surface was covered with a polyglycolic acid sheet and plasma derivative.
The resected specimen measured 30 × 30 × 10 mm in size, and a soft and elastic mass measuring 10 mm × 10 mm in size was seen in the central submucosa. The histopathological findings showed existing small salivary gland tissue was seen from the submucosal layer to within the muscle layer multifocal nodal lesions similar to the replacing replaced salivary gland lobules. There was adhesion of epithelial components with glandular cavity structures in the interior of the nodular lesions, consisting of sites made up of cribriform structures and partially solid regions. Immunohistologically, a majority of the cancer cells were positive for Cytokeratin AE1/AE3 (CKAE1/AE3), Cytokeratin CAM5.2 (CAM5.2), Cytokeratin19 (CK19), S-100 protein, and mammaglobin and negative for anti-smooth muscle antibody, calponin, carcinoembryonic antigen, human epidermal growth factor receptor 2, and discovered on gastrointestinal stromal tumor 1 (DOG1) (Figure 3). Secretory carcinoma was suspected from pathologically and immunohistological characteristics, and the ETV6-NTRK3 fusion gene was detected in a gene search. Based on the above findings, the definitive diagnosis was secretory carcinoma. The patient was followed and at 9 months postoperatively there was further enlargement of the left submandibular lymph nodes, which had been enlarged from before the surgery. Fine needle aspiration biopsy led to a diagnosis of Class III, and lymph node metastasis of the secretory carcinoma was suspected. A left neck dissection (Level 1-V) was performed in June 2017. Metastasis was seen in a submandibular lymph node, and

**Figure 3.** Histopathological and immunohistological findings. (A) Multifocal nodular lesions are seen similar to replaced the salivary gland lobules. Epithelial components with glandular cavity structures adhere in the interior of these lesions, which consist of sites made up of cribriform structures and some solid regions (HE stain); (B) Representative image of a mammaglobin-positive area; (C) Representative image of an S-100 protein-positive area; (D) Representative image of a DOG1-negative area.
the histopathological findings showed a histological presentation similar to left buccal mucosal secretory carcinoma. Cervical lymph node metastasis secondary to secretory carcinoma was diagnosed. No recurrence has been seen for 1 year and 6 months postoperatively.

4. Discussion

MASC is a salivary gland malignancy for which the disease concept has been recently established. In 2002, Hirokawa et al. [3] reported that it is histologically a subtype of breast cancer that produces mammary gland secretions and resembles secretory carcinoma of the breast, a low-grade adenocarcinoma that presents varied images. Its morphology and immunostaining characteristics resemble some acinic cell carcinomas (AciCC). In 2010, Skalova et al. discovered that the ETV6-NTRK3 fusion gene is seen in both secretory carcinomas of the breast and AciCC with similar characteristics, and they proposed MASC as a novel disease. MASC was newly classified as a secretory carcinoma in the 2017 WHO classification of salivary gland tumors (4th edition).

The gross and histopathological characteristics of secretory carcinoma are that most of the tumor consists of a solid portion, while occasionally large cystic cavities also form. Histologically, it shows solidity infiltrated with very small cystic cavities and cribriform and papillary features and includes periodic acid-Schiff stain-positive, acid-fast secretions. The cells have oval nuclei, and vacuolated cytoplasm and foamy secretions are seen. Anaplasia is not strong and mitotic figures are rarely seen [4]. These features closely resemble AciCC. Immunohisto logically, it is thought to be positive for S-100 protein [1] [4] [5] [6], vimentin, [1] [4] [6] [7] and mammaglobin [1] [4] [5] [8] and negative for DOG1 [9] [10]. Nermine et al. [11] reported that all 9 patients with AciCC were negative for DOG1. Thus, S-100 protein, mammaglobin, and DOG1 are considered to be very useful in differentiating MASC from other salivary gland malignancies, including secretory carcinoma and AciCC. Recently, it has been reported that the ETV6-NTRK3 fusion gene has not been detected in any salivary gland tumors other than secretory carcinoma. The presence of the ETV6-NTRK3 fusion gene is essential in diagnosing secretory carcinoma [12] [13]. In the present case, multifocal modular lesions were seen histopathologically, as if replacing the lobules of the salivary glands. Inside these lesions, adhesion of epithelial components with glandular cavity structures, consisting of sites made up of cribriform structures and partially solid regions were seen. This is a finding that markedly resembles AciCC. Immunohistologically, the tumor was positive for mammaglobin and S-100 protein and negative for DOG1. Hence, secretory carcinoma was strongly suspected and the ETV6-NTRK3 fusion gene was positive. The patient was finally diagnosed with left buccal submucosal secretory carcinoma.

Sethi et al. [2] analyzed 92 patients with secretory carcinoma and reported their clinical features. The female to male ratio is about 1.2:1 and the mean age was 44.2 years. The tumors often grow painlessly. The primary site of onset is the parotid gland (70%), followed by the submandibular gland (7%). Occurrence
in the minor salivary glands in the soft palate, buccal mucosa, base of the tongue, and lips has been previously reported. Chiosea et al. [5] reported cervical lymph node metastasis from secretory carcinoma in 22% of cases (four of 18), recurrence in three cases (three of 18), and distant metastasis in one case (one of 18). Although malignancy is somewhat higher in secretory carcinoma than in AciCC, no significant difference is seen between the two diseases in the disease-free survival rate and treatment success rate. Secretory carcinoma is difficult to diagnose clinically and cytologically, and when a low-grade malignancy such as AciCC is suspected clinically, it is important to consider secretory carcinoma in consultation with a pathologist when making a diagnosis. Cervical lymph node metastasis is also somewhat more common in secretory carcinoma than in AciCC and was seen in our patient. Thus, a careful examination for cervical lymph node metastasis and subsequent neck dissection without delay in metastasis cases are thought to be important. Although secretory carcinoma is generally considered to be a low-grade malignancy, sarcomatoid changes and poor outcomes are seen in some cases and careful examination and follow up is needed [14].

The disease concept of secretory carcinoma has been recently established. Currently, the first-line treatment is surgical resection, similar to other salivary gland malignancies [15]. However, the anaplastic lymphoma kinase (ALK) inhibitor crizotinib has been reported to significantly reduce ETV6-NTRK3 gene fusion, and it is potentially effective in the treatment of secretory carcinoma [16]. It is necessary to accumulate further elucidation of the pathology of this malignancy in a greater number of patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


A Case Report of Double Malignancy—Recurrent Nasopharyngeal Carcinoma and Adenocarcinoma of the Uterus

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Abstract
Multiple primary malignancies (MPMs) is a rare clinical condition where a patient is diagnosed with two or more cancers around the same time. Published literature reported the incidence of multiple primaries is in the range of 2% - 17%. The risk factors for MPMs are smoking, chronic alcoholism, genetic factors and previous treatment of cancer using radiotherapy that may lead to the development of other cancer. This case report describes a rare and unfortunate case of middle-aged Malaysian Chinese lady diagnosed with adenocarcinoma of the uterus and around the same time she had a recurrent nasopharyngeal carcinoma which was first diagnosed and treated 11 years ago. There were no clear risk factors identified in her and she defaulted follow up which eventually led to a fatal complication in which the nasopharyngeal cancer caused massive bleeding in her and she finally succumbed to the complication despite emergency resuscitations.

Keywords
Multiple, Primary, Malignancies

1. Introduction
Multiple primary malignancies (MPMs) are diagnosed when more than one primary malignancy arising in different sites and/or they are of a different histology or morphology group. This clinical entity is not that common, the worldwide reported frequency of multiple primaries ranges from 2% - 17% [1].

According to International Agency for Research on Cancer, when more than one tumor is confirmed in a patient at the same time or within six-month period
is known as synchronous tumor and if another tumor is diagnosed after a period of 6 months is known as metachronous [2].

The actual etiology of MPMs remain unknown but many epidemiological studies have documented MPMs are highly associated with chronic smoking, family history of malignancies, genetic susceptibility, previous exposure to radiation or chemicals and some clinical syndromes such multiple endocrine neoplasm (MEN) 1 and MEN 2 [3] [4]. However, in individuals confirmed with MPMs, very often no significant risk factors are identified.

The following case described a rare and unfortunate case of middle-aged Malaysian Chinese lady who was diagnosed with adenocarcinoma of uterine and around the same time diagnosed with a recurrent nasopharyngeal carcinoma (synchronous tumor) eleven years after the first diagnosis.

2. History

A 51-year-old Malaysian Chinese housewife who was diagnosed with nasopharyngeal carcinoma 11 years ago (in 2007) at the age of 40 years old, She completed radiotherapy treatment; however, she developed the complication of bilateral osteoradionecrosis. Few months into the follow up, she defaulted treatment and her clinical status and progress were unknown since then. There was no history of smoking, alcohol or any known family members diagnosed with cancer.

In early July 2018, which was 11 years after the initial diagnosis of nasopharyngeal carcinoma, she presented to the community clinic with the problem of heavy menses which lasted longer than her usual normal period for almost 6-month duration. She was then referred to gynecologist for further evaluation. Ultrasonography showed intrauterine mass and an endometrial tissue sampling confirmed adenocarcinoma of the uterus. Stage 1A, she underwent laparoscopic hysterectomy and bilateral salphingo-oophorectomy, which was also followed by four cycles of chemotherapy. The surgery was successful, and the recovery was uneventful.

About 8 weeks following the diagnosis of endometrial cancer she presented again to the community clinic with a new complaint of right facial swelling and intermittent epistaxis for two weeks duration. Subsequently she was referred to the Department of Otorhinolaryngology in a tertiary hospital for further evaluation. Examination of the nasal cavity revealed presence of a soft tissue mass in the right nasal cavity. Facial computer tomography (CT) was requested and it showed a heterogeneous enhancing mass measuring about 5 × 5 cm at the right nasopharynx with local infiltration involving the sinonasal (Figure 1 and Figure 2), oral region and intraorbital region (Figure 3 and Figure 4). There were also intramuscular infiltrate and surrounding bony erosion. There was no intracranial involvement and no lung or liver metastasis. A tissue biopsy was obtained, and subsequent histopathological report confirmed squamous cell carcinoma arising from the nasopharynx.
Figure 1. Sagittal CT showed nasopharyngeal tumor infiltrated into the right sinonasal, intraorbital region with bony erosion.

Figure 2. Coronal view of the nasopharyngeal tumor occupying the entire right nasal cavity.

Figure 3. Inferiorly the tumor infiltrate to oral cavity.
3. Progress and Outcome

The patient was referred to oncology unit for further management and was under the multidisciplinary care comprises the otorhinolaryngologist, gynecologist and oncologist. She was planned for chemotherapy for the recurrent of nasopharyngeal carcinoma. However, due to some personal factors, she defaulted the follow up and treatment appointment. Four weeks later, on one evening she was brought by the daughter to the hospital emergency department in an unconscious state. The daughter described the mother had a sudden massive bleeding two hours prior coming to hospital. On examination, blood was actively oozing from her nose. She was pale and hemoglobin detected was 6 grams per deciliter. Her blood pressure was 70/40 mmHg, pulse 120 beats/minutes. Despite of active transfusion and resuscitation, patient succumb to her illness two hours later. The cause of death reported as hypovolemic shock secondary to massive intranasal hemorrhage due to underlying recurrent nasopharyngeal carcinoma.

4. Discussion

Multiple primary malignancies are a rare clinical condition. It is even rarer to have malignancies involving both the nasopharyngeal region and the uterus diagnosed around the same time. Within the region of South East Asia, it was reported by Singapore Cancer Registry that multiple primary cancers account for only 0.38% of all cases in their registry. It also documented there were few cases of nasopharyngeal carcinoma occurring together with uterine cervical cancer. Epstein-Barr virus could be the possible etiological agent and further study need to be conducted to look at its association especially among the Chinese lady in this region [5] [6]. Many pathological studies showed cervical epithelium is known to contain receptors for Epstein-Barr virus (EBV) and is a recognized site of viral shedding. More recent cases of nasopharyngeal carcinoma have been associated with cervical carcinoma, thus the hypothesis that EBV and cervical carcinoma...
are both related [6] [7].

As with many other multiple primary malignancies reported elsewhere, the patient presented in this case did not have any significant risk factors such as smoking or drinking alcohol. None of her family members was diagnosed with cancer. The only significant past history was she had radiotherapy 11 years ago for her first diagnosed nasopharyngeal carcinoma. However, there was no strong evidence to suggest this led to her uterine cancer after 11 years. No laboratory test performed in her to indicate any association with exposure to Epstein-Barr virus. The occurrence of multiple primary malignancies in this patient could be multi-factorial.

The prognosis and survival of multiple primary malignancies depends very much on the cancer type and also the stage at the time of diagnosis. Among other factors affecting the prognosis include genetic factors, behavioral influences, lifestyle and comorbid illnesses [8].

The most important poor prognostic factor in this particular patient which we highlighted was non-compliant to treatment. Despite of appointment for treatment and follow-up was given, she defaulted. No specific reason was given by patient or her family members as why she failed to turn up for the treatment. Following defaulting treatment, the tumour most likely had infiltrated nearby blood vessels, therefore she presented with massive uncontrollable bleed. Adequate health education remains an important factor in this region. The treating physician should be encouraged to spend more time to explain and advice the patient especially in a case of multiple primary malignancies which required close follow-up and multidisciplinary approach in the management.

5. Conclusion

Multiple primary malignancies (MPMs) is a rare clinical condition, nevertheless any patient diagnosed and treated for malignancy if presents with new clinical symptoms, the treating physician must look for the evidence of recurrence and possibility of multiple malignancies. In such circumstances, the patient usually needs multidisciplinary approach and proper advice and counseling to patient and family is necessary to ensure good response to treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


Head and Neck Cancer Early Identification of Malnutrition High Risk Patients and Quality of Life Optimization

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Abstract

Malnutrition in Head and neck cancer (HNC) patients can be present at the moment of diagnosis. The nutritional status is determinant for the treatment success and quality of life of the patients. The nutritional status gradually declines during treatment and the majority of patients undergoing treatment will need nutritional therapy. On the other hand, HNC, like other cancers, can induce a paraneoplastic syndrome that leads to cachexia. This cachexia status is most of the times the cause of death or the cause of treatment failure. So, early identification of malnutrition high risk patients is crucial to start an adequate nutrition support intervention in HNC patients. This study aims to identify HNC patients who present malnutrition or higher risk of malnutrition; to signalize variables that support early identification of high-risk patients of becoming malnourished and to establish a dynamic relationship between malnutrition risk in these patients and Quality of Life (QoL) impacts.

For six months consecutive outpatients with HNC admitted at the Head & Neck Unity of Oncology Portuguese Institute—Porto were asked to participate in the research (n = 114). The European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific HRQoL questionnaire-QLQ-C30 and Malnutrition Universal Screening Tool, MUST were used. At the moment of first presentation, 32 patients (28.1%) presented high-risk of malnutrition. HNC patients with oral cavity and oropharynx tumour locations, older, with low literacy or with BMI under 18.5 at the moment of diagnosis, represent a high-risk group. When HNC is considered, a dynamic and bi-directional connection between malnutrition and QoL is observed. A significant (p < 0.001) difference in the scores of Global health status/QoL according to the malnutrition risk group was found: 62.96, 53.33, 42.71 for low, medium and
high malnutrition risk respectively. Also, Emotional and social functional scales and all symptom scales—including pain, presented significant differences between high and medium risk of malnutrition patients. Fatigue, pain, insomnia, appetite loss and financial difficulties were domains directly related to high risk of malnutrition patients. Pain scores were significantly higher (43.23) in the high-risk patients when compared to medium risk patients (11.67). Nutrition support should be considered at any stage of the pathway—especially in high risk group—in order to optimize tumour treatment results, reduction of adverse effects of therapy and improving both QoL and survival.

Keywords
Oncology, Head and Neck Cancer, Body Mass Index Malnutrition, Nutritional Support, Quality of Life, Malnutrition Universal Screening Tool

1. Introduction

Head and neck cancer (HNC) accounts for more than 550,000 cases and 380,000 deaths annually [1]. In the United States 63,000 new cases occur every year while in Europe a higher incidence is seen—250,000 new cases per year. HNC squamous cell carcinoma represents 3% and 6% of all cancer cases respectively [2] [3] [4].

HNC comprehends several locations: the oral cavity, pharynx, larynx, paranasal sinuses and salivary glands and is necessarily related to malnutrition during the disease process and the treatment [5].

Studies reveal that tumour locations, cancer stage, treatment plan, dietary habits, initial weight and body mass index (BMI), lifestyle factors, alcohol and tobacco consumption, oral health performance, social conditions, financial circumstances and cachexia syndrome can guide HNC patients to malnutrition [6] [7] [8].

Significant weight loss and resultant malnutrition caused by a decrease in food intake are expected in HNC patients undergoing radiotherapy. Additionally, poor oral health and chemotherapy act as co-factors in HNC undernourishment. Still, head and neck surgery may cause swallowing dysfunction, xerostomia and severe dysphagia leading to underfeeding. At diagnosis, 20% - 67% HNC patients are malnourished or at high risk of becoming malnourished. The malnutrition prevalence rate of HNC patients overtakes 80% [9] [10] [11].

This aspect is often associated with weight and muscle loss, decrease functioning, depression and negative impacts in Quality of Life (QoL). HNC patients often present delayed wound-healing, oedema and reduced response to chemotherapy and radiotherapy being the effective curative treatments often unsatisfactory. Malnutrition is still linked to increased risk of infection and post-operative complications. Patients malnourished present higher mortality rates and urgent hospital readmissions with economic implications [5] [6] [8] [12].
Early identification of high-risk patients and intervention with nutrition support is crucial in HNC [11].

1.1. Objectives

This study aims to:

- Identify HNC patients who present malnutrition or higher risk of malnutrition;
- Signalize variables that support early identification of high-risk patients of becoming malnourished;
- Establish a dynamic relationship between malnutrition risk in HNC patients and QoL impacts.

1.2. Method

Ethics

The study was carried out in compliance with the Helsinki Declaration. The method was previously approved by the local research ethical committee and all HNC patients agreed to participate in the research and gave their informed consent. The data were collected for research purposes as part of the routine evaluation.

Patients

For six months, between January and June 2015, consecutive outpatients with HNC admitted at the Head & Neck Unity of Oncology Portuguese Institute—Porto (IPOP) were asked to participate (n = 114).

Socio-demographic data and clinical data—age, gender, education, body mass index (BMI), involuntary weight loss, malnutrition risk (Malnutrition Universal Screening Tool, MUST), and tumour location—were collected from the patient’s clinical process and complemented, when needed, in semi-structured interviews with patients, proxies or clinical staff. In order to better understand socio-demographic and clinical variables, patients were divided in three groups based on MUST risk (low, medium and high).

Questionnaires and scales

The European Organisation for Research and Treatment of Cancer (EORTC) cancer-specific HRQoL questionnaire-QLQ-C30, were used (Portuguese validated versions).

Questionnaires were completed immediately before consultation as a part of the routine evaluation. Inclusion criteria were: ability to understand written and spoken Portuguese and provision of written consent and physical presence in IPOP for consultation in Head and Neck Unity in the research days.

MUST risk was assessed using three parameters: current BMI, unintentional weight loss and the presence of any acute disease effect that could compromise nutritional intake for >5 days. These parameters are rated 0, 1 or 2 as follows: BMI > 20 kg/m² = 0, BMI between 18.5 and 20.0 kg/m² = 1 and BMI < 18.5 kg/m² = 2; unintentional weight loss in the past 3 - 6 months < 5% = 0, weight loss between 5% and 10% = 1 and weight loss > 10% = 2; acute disease absent = 0 or acute disease present = 2.
The overall risk of malnutrition is defined by the sum of all points allocated to each parameter and is classified as follows: 0 = low-risk; 1 = medium-risk; 2 = high-risk [13].

**Analysis Strategies and Statistics**

Completed questionnaires were scored according to EORTC instructions. Health-related QoL data were analysed by the Statistical Package for Social Sciences (SPSS), version 17 for Windows. Descriptive data are presented with means, standard deviations, medians, ranges, and proportions as appropriate. The chi-squared test was used for testing relationships between the studied variables and to determine whether if there was a significant difference between the expected frequencies and the observed frequencies in the studied variables.

**1.3. Results**

**1) HNC Patients’ Characteristics**

Sociodemographic and clinical characteristics of the studied sample is presented in Table 1 (n = 114). Patients were mainly male (93.9%) and the majority was

<table>
<thead>
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<th>Table 1. Head and neck cancer patients characteristics (n = 114).</th>
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<td><strong>Education</strong></td>
</tr>
<tr>
<td>≤6 years</td>
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<tr>
<td>&gt;6 years</td>
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</table>
46 – 65 years old (63.2%), revealed low-risk of malnutrition (63.2%), a BMI greater than 18.5 (89.5%) and a low educational level (only 24.6% completed more than 6 schooling years). Hypopharynx and larynx were found to be the major tumour locations (53.5%).

2) Early identification of high risk of malnutrition in HNC patients according to age, tumour location, BMI and education

As depicted in Table 2, we found clear relationship between patient’s age and the risk levels of malnutrition: high-risk patients were significantly younger than the low-risk malnutrition group (p = 0.007) and less heterogeneous (51.94 ± 6.56 and 58.94 ± 12.66, respectively) presenting a lower age range (from 39 to 64 years old).

An association between tumour location and the risk of malnutrition was identified (Chi-squared = 20.287 degrees of freedom = 4, p = 0.000). Indeed, the high-risk malnutrition group presented greater tumour incidence in oral cavity & oropharynx (15 cases observed compared to 10.7 expected) and revealed an incidence in hypopharynx and larynx locations as expected (16 cases observed similar to 17.1 expected).

It was found an association between BMI and the risk for malnutrition (Chi-squared = 26.884; degrees of freedom = 2; p = 0.000). Indeed, all patients but one, presenting a BMI lower than 18.5 , belonged to the high-risk group for malnutrition.

A relation between education and the risk for malnutrition was detected (Chi-squared = 6.763; degrees of freedom = 3; p = 0.034) as depicted in Table 2. In fact, higher education (more than 6 schooling years) was associated with a low-risk of malnutrition—this group presented fewer patients than expected with high-risk of malnutrition (ratio 0.63) and more patients than expected in

| Table 2. Early identification of MUST risk in HNC patients (n = 114) according to age, tumour location, BMI and education (Chi-squared test was used,*p < 0.005; **p < 0.001; Low, n = 72; Medium, n = 10; High, n = 32). |
|-----------------|-----------------|-----------------|-----------------|
| **MUST risk**   | **Low**         | **Medium**      | **High**        |
| **Age** mean ± SD (n) | 58.94 ± 12.66 (72) | 52.20 ± 11.34 (10) | 51.94 ± 6.56 (32)* |
| **Tumor location** % (n) | | | |
| Oral cavity & oropharynx | 13.16 (15) | 7.02 (8) | 13.16 (15) ** |
| Hypopharynx & larynx | 37.72 (43) | 1.75 (2) | 14.04 (16) |
| Other | 12.28 (14) | 0.00 (0) | 0.88 (1) |
| **BMI % (n)** | | | |
| >18.5 | 62.28 (71) | 8.77 (10) | 18.42 (21) |
| <18.5 | 0.88 (1) | 0.00 (0) | 9.65 (11)** |
| **Education** % (n) | | | |
| Up to 6 years (n = 86) | 42.98 (49) | 8.77 (10)* | 23.68 (27)* |
| More than 6 years (n = 28) | 20.18 (23)* | 0.00 (0) | 4.39 (5) |
the low-risk group of malnutrition (ratio 1.30). On the contrary, the less educated group proved to be more vulnerable to malnutrition risk, having more patients than expected both in the high-risk group (ratio 1.12) and in the medium-risk group of malnutrition (1.33).

3) Malnutrition risk in HNC patients and QoL impacts

It was found that the risk of malnutrition has consistent impact on QoL (Table 3).

Patients at high-risk of malnutrition revealed a constant and significantly lower mean score in Global health status and in QoL. A median of 42.71 was found for high-risk patients group significantly lower than the median found low or medium risk groups, with 62.96 and 53.33 respectively.

When we look for all functional scales—and therefore worse QoL and functioning—the results are comparable, showing lower scores in the high-risk group of patients.

Similar trend was found when considering all symptoms scales where the higher scores—reflecting greater symptomatology—were always found in this group (high-risk).

When considering the functional scales, no differences were found between medium and low risk patients. But for Role, Emotional and Social Functioning scales, significant differences (p < 0.001) occurred between high and medium patient’s risk (median scores of 66.15, 65.63 and 77.08 for high-risk patients and 96.67, 90.00 and 96.67 for medium-risk patients when considering Role, Emotional and Social Functioning scales respectively).

Table 3. Impact of malnutrition (MUST risk) on HNC patient’s QoL assessed by EORTC QLQ C-30 (Chi-squared test was used; Low, n = 72; Medium, n = 10; High, n = 32).

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status/QoL</td>
<td>62.96 ± 23.73</td>
<td>53.33 ± 23.31</td>
<td>42.71 ± 24.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>82.72 ± 16.39</td>
<td>86.67 ± 7.70</td>
<td>75.00 ± 17.60</td>
<td>0.014</td>
</tr>
<tr>
<td>Role functioning</td>
<td>89.12 ± 20.01</td>
<td>96.67 ± 10.54</td>
<td>66.15 ± 36.30</td>
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<tr>
<td>Emotional functioning</td>
<td>79.17 ± 17.47</td>
<td>89.17 ± 13.06</td>
<td>65.63 ± 26.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>91.67 ± 13.12</td>
<td>90.00 ± 8.61</td>
<td>79.69 ± 24.22</td>
<td>0.004</td>
</tr>
<tr>
<td>Social functioning</td>
<td>92.13 ± 13.98</td>
<td>96.67 ± 7.03</td>
<td>77.08 ± 27.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14.35 ± 15.66</td>
<td>14.44 ± 20.32</td>
<td>34.72 ± 25.04</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2.32 ± 7.56</td>
<td>1.67 ± 5.27</td>
<td>7.81 ± 16.93</td>
<td>0.052</td>
</tr>
<tr>
<td>Pain</td>
<td>15.75 ± 23.18</td>
<td>11.67 ± 13.72</td>
<td>43.23 ± 29.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1.36 ± 0.64</td>
<td>1.10 ± 0.32</td>
<td>1.66 ± 0.90</td>
<td>0.049</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.76 ± 0.91</td>
<td>1.70 ± 1.06</td>
<td>2.56 ± 1.01</td>
<td>0.001</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>1.39 ± 0.66</td>
<td>1.50 ± 0.71</td>
<td>2.09 ± 1.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.19 ± 0.55</td>
<td>1.00 ± 0.00</td>
<td>1.72 ± 1.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.14 ± 0.39</td>
<td>1.00 ± 0.00</td>
<td>1.06 ± 0.25</td>
<td>0.332</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>1.29 ± 0.39</td>
<td>1.60 ± 1.08</td>
<td>2.13 ± 0.88</td>
<td>0.001</td>
</tr>
</tbody>
</table>
In symptom scales, scores were always higher in the high risk of malnutrition group, revealing to be significantly different from the low risk of malnutrition group except for Diarrhoea and Nausea and vomiting.

The major associations were found in Fatigue, Pain, Insomnia, Appetite loss and Financial difficulties symptoms \((p = 0.001\)). Moreover, Fatigue, Pain, Insomnia and Constipation symptom’s differences also occurred between high and medium risk patients. A particularly significant difference verified was in Fatigue and Pain scales, with median scores for high-risk patients of 34.72 and 43.23 and median scores for low-risk patients of 14.35 and 15.75, respectively. The same differences were encountered for medium-risk patients (median scores of 14.44 for Fatigue scale and 11.67 for Pain scale).

Just like in the functional scales, when considering the symptom scales, no differences were found between medium and low risk patients.

2. Discussion

HNC patient’s demographic patterns have been changing over the past 30 years—they are more likely to be younger adults in their 40s and 50s who never smoked or had reduced tobacco exposure. It is suggested that 70% - 90% of new cancers are oropharyngeal, an evidence of the human papillomavirus (HPV) \([14]\). The studied sample does not follow such trend since patients are older (63.2% having 46 - 65 years old) and the major tumour location was not oropharyngeal but hypopharynx and larynx.

These findings may reflect a limitation of our study because patients were included while they have been presented to first time consultation in our department for a consecutively period of 6 months. So, this study population may not reflect the real incidence of HNC in Portugal when we are looking for some demographic data or incidence according to HNC primary sites.

Pharynx, larynx, and oral cavity tumour location is a predictor of greater weight loss. Side effects are related to HNC, mainly in oral cavity and oropharynx tumour locations: dysphagia and odynophagia, oral mucositis, dry mouth, taste loss, trismus, muscles fibrosis, ulcerations, teeth loss, chewing and swallowing difficulties \([8]\) \([15]\) \([16]\) \([17]\).

More than half of the problems influenced by HNC have some connection with nutritional problems. Eating-related problems (oral pain, fit of the dental prostheses, prolonged eating time, reduced eating pleasure, and not being able to eat with family and friends) usually appear early and often even before diagnosis (20% - 67% are malnourished or at high risk of becoming malnourished at diagnosis). So, malnutrition high risk in HNC patients can happen at presentation and the nutritional status gradually declines during treatment and most patients undergoing treatment will need nutritional therapy \([8]\) \([15]\) \([16]\) \([17]\).

We found the majority of HNC patients had low risk of malnutrition (63.2%), a clear contrast to values often described in the literature referring up to 80% malnourished because of their lifestyle and the risk factors associated with this...
disease [18]. Such difference may be explained by the fact that assessment occurred when patients were admitted at the Head & Neck Unity, before any treatment [19] [20].

Nutritional assessment supports and institutional awareness, may favour early nutritional intervention on nutritional status [21] [22]. Awareness of this fact is of major importance when establishing a treatment and follow-up schemes in HNC patients.

HNC are a naturally diverse group of tumours linked by anatomical proximity [4]. HNC patients are commonly associated with low patient health literacy as a result of poor education and socioeconomic status [23] [24]. Indeed, the low patient’s literacy level found (only 24.6% completed more than 6 schooling years) reinforces this idea and adds new challenges. Once more the patient recruiting process used in our study can be a limitation when looking to this data because of the possible bias in the population selected.

Certainly, with an aging population and advances in diagnosis and treatment, the number of patients living with the effects of HNC and its treatment continue to rise. Thus, literacy and educational support for both patients and caregivers, particularly in areas of survivorship, are important to optimize well-being [25] [26].

BMI should be always considered when analysing HNC patients in order to follow weight loss described during treatments [27]. An association between BMI and survival has been described [28]. The BMI observed, greater than 18.5 for the vast majority of the studied patients (89.5%) seems thus to constitute a positive prognostic factor. On the other hand, as said before, the recruiting process used in our study may not represent with accuracy the true HNC patients in Portugal. But in this case we don’t see this as a limitation of our study because the purpose of the study was to see the relationship of the malnutrition risk in HNC patients and its impact on QoL.

In the present study, patients at high risk of malnutrition revealed a constant and significantly poor QoL in multiple domains. Nutritional status is a strong predictor for HNC patients’ QoL before, during and after treatment. Weight loss and malnutrition conduces to nutritional interventions: oral, enteral and parenteral and immune-enhanced nutrition. Tube feeding, usually an invasive procedure, is associated with extended hospitalization, QoL negative impacts and risk of mortality. On the other hand, oral nutritious supplements may introduce several problems: decrease salivary flow and quality, reduce oral clearances, increase bacteria colonization, risk of oral diseases or oral dehydration. QoL domains, such as: swallowing, taste and smell, sticky saliva, mouth pain, speech problems, discouragement or feeling ill, are commonly affected by nutritional interventions. Percutaneous endoscopic gastrostomy, used when long-term tube feeding is necessary, is associated with improved QoL. Quality of nutritious supplements make all difference: the ideal oral supplement should be ready-to-eat, most resemble to regular food (solid like), chewable, moisten, and easy to swallow [15].
Our study shows that patients with high-risk for malnutrition have low scores for Global QoL. So routine QoL evaluation, complementing the usual follow-up schemes, is a good surveillance tool and an eventually a good nutritional indicator.

*Emotional and social functioning scales and all symptom scales* presented significant differences between high and medium risk of malnutrition patients. Functional impairments and psychological distress are common in HNC (20% - 60% of patients have depressive symptomatology two to three months post-diagnosis). In the present study, *fatigue, pain, insomnia and appetite loss* were domains particularly associated to high risk of malnutrition group. There is a dynamic and reciprocal association between QoL domains (depressive and anxiety symptoms, pain, nausea, fatigue, appetite) and weight loss. Pain is considered a robust predictor of poorer QoL in HNC [7] [32] [33].

In this study we can state that pain is the most limitation related to malnutrition. Our data shows that patients in the high-risk group for malnutrition have poorer scores on *Pain scale* and the impact only occurs in this group (low and medium risk group of patients have similar scores in *Pain scale*). Future development of this finding could relate QoL evaluation, pain control and analgesics consumption, with nutritional status.

Lifestyle mediation (nutritional and psychosocial support, physical activity orientation) at the moment of diagnosis has been recognized as an important intervention, helping patients to manage side effects and improve their QoL [5].

HNC patients should be subject to a plan contemplating early identification of malnutrition high risk and nutrition interventions. Comprehensive nutritional assessment, documentation, weight loss follow-up and QoL evaluation should be include since admission. It would contribute to identify different needs during the disease trajectory in order to ensure appropriate interventions. Effective nutritional interventions should ultimately aim to improve QoL [16] [17] [19] [22] [34].

### 3. Conclusions

HNC patients are a recognized high-risk group for malnutrition and the diagnostic criteria used to define patients as malnourished lacks uniformity. Perform pre-treatment nutrition and QoL assessments allows early identification of high-risk patients representing a fundamental step to identify nutrition status at baseline, in order to improve it during and after treatments.

HNC patients with oral cavity and oropharynx tumour locations, older, with low literacy or with BMI under 18.5 at the moment of diagnosis, represent a high-risk group.

When HNC is considered, a dynamic and bi-directional connection between malnutrition and QoL is observed. *Emotional and social functional scales and all symptom scales*—including *pain*, presented significant differences between high and medium risk of malnutrition patients. *Fatigue, pain, insomnia, appetite loss*
and financial difficulties were domains directly related to high risk of malnutrition patients.

Nutrition support should be considered at any stage of the pathway—especially in high risk group—in order to optimize tumour treatment results, reduction of adverse effects of therapy and improving both QoL and survival.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


https://doi.org/10.1017/S0022215116000402
Thyroid Cancer

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Abstract

Thyroid tumors include those that originate from follicular cells and those that arise from parafollicular cells (C cells). Differentiated thyroid cancer, which originates from follicular cells, includes papillary carcinoma, follicular carcinoma, oncocytic cell carcinoma (Hürthle), poorly differentiated carcinoma, and anaplastic carcinoma. The incidence of thyroid cancer has been increasing significantly, with an estimated incidence in the United States of America of 53,990 cases by the year 2018. This neoplasm is listed as the most common endocrine tumor and represents approximately 3% of all malignant tumors in humans, with 75% of cases occurring in women, and two-thirds of cases occurring in people under 55 years. The increase in the prevalence/incidence of low-risk thyroid cancer over the last 10 to 20 years has required a re-appraisal of the standard one-size-fits-all approach to differentiated thyroid cancer. This adaptation to a more individualized management of the patient with thyroid cancer has led to a much more risk-adapted approach to the diagnosis, initial therapy, adjuvant therapy, and follow-up of patients with differentiated thyroid cancer. This paper will review the current understanding of the clinical presentation, diagnostic workup, and management of thyroid cancer centered on evidence-based and personalized medicine.

Keywords

Thyroid Nodules, Thyroid Cancer, Thyroid FNA, Thyroid Nodule Workup, Thyroid Cancer Treatment, Molecular Studies for Thyroid Cancer

1. Introduction

Thyroid nodules are a major public health problem. Epidemiological studies have shown that the prevalence of palpable thyroid nodules is approximately 5% in women and 1% in men living in parts of the world with sufficient iodine [1]
In contrast, high-resolution neck and thyroid ultrasound can detect thyroid nodules in approximately 19% to 68% of randomly selected people, with higher frequencies in women and the elderly [3] [4]. The clinical importance of thyroid nodules lies in the need to exclude thyroid cancer, which occurs between 7% and 15% of cases, depending on age, sex, radiation exposure history, family history, among other factors [5] [6].

Thyroid neoplasms include those that originate from follicular cells and those that arise from parafollicular cells (C cells). Differentiated thyroid cancer, which originates from follicular cells, includes papillary carcinoma, follicular carcinoma, oncocytic cell carcinoma (Hürthle), poorly differentiated carcinoma, and anaplastic carcinoma. These thyroid tumors comprise the vast majority (more than 90% of cases) of all thyroid cancers [7]. Of these subtypes, anaplastic carcinoma is rare and is characterized by its extremely poor prognosis. Similarly, poorly differentiated carcinoma is characterized by its aggressive behavior and its unfavorable prognosis. Between 2010 and 2014, 63,229 patients per year were diagnosed with thyroid carcinoma. Of these 63,229 patients, 89.4% had papillary carcinoma, 4.6% had follicular carcinoma, 2.0% had oncocytic cell carcinoma, 1.7% had medullary carcinoma, and 0.8% had anaplastic carcinoma [8].

The incidence of thyroid cancer has been increasing significantly since the mid-1990s, with an estimated incidence in the United States of America of 53,990 cases by the year 2018 [9]. This cancer is listed as the most common endocrine neoplasm and represents approximately 3% of all malignant tumors in humans, with 75% of cases occurring in women [9] [10], and two-thirds of cases occurring in people under 55 years [9]. Less aggressive forms of these tumors are more common in women and younger people [8]. The thyroid cancer mortality rate has remained stable in women but has increased by approximately 1% per year since 1983 in men and will be responsible for approximately 2060 deaths in 2018 [9]. The relatively low mortality rate compared to the incidence is due, in part, to the indolent nature of the vast majority of thyroid tumors. Patients with differentiated thyroid cancer generally have an excellent long-term prognosis, with five-year survival rates close to 100% for localized disease [8]. Despite the low mortality rates, local recurrence occurs in approximately 20% of patients, and distant metastases occur in about 10% of patients 10 years after diagnosis [11]. Mortality from thyroid cancer has been increasing in the last 18 years [8], which is why progress in the development of new systemic therapies for thyroid cancer refractory to iodine is extremely important. We know that medical development in this field has been delayed compared to the progress observed in the treatment of other solid tumors, however, data from emerging clinical studies suggest that thyroid cancer can be treated with targeted agents, particularly kinase inhibitors, with promising results that overshadow those previously seen with cytotoxic agents [12].

The annual incidence of thyroid cancer has almost tripled from 4.9 cases per 100,000 people in 1975 to 14.3 cases per 100,000 people in 2009 [13]. Almost all of the change has been attributed to an increase in the incidence of papillary
thyroid cancer [8] [9] [13]. 25% of new thyroid tumors diagnosed between 1988 and 1989 were equal to or less than 1 cm in diameter compared to 39% of new thyroid tumors diagnosed between 2008 to 2009 [13]. This may be due to the increasing use of high-resolution neck ultrasound and other diagnostic imaging techniques leading to finding asymptomatic thyroid lesions (incidentalomas), trends that are changing the initial treatment and follow-up of many patients with thyroid cancer [14].

The detection and diagnosis of differentiated thyroid cancer has evolved over the years with increased use of high-resolution neck and thyroid ultrasound, fine needle aspiration biopsy (FNAB), molecular tests, and thyroglobulin as a serum marker. This evolution has led to greater controversy regarding the appropriate medical and surgical management of this cancer. The type of surgical resection (lobectomy vs. total thyroidectomy), the role of lymphadenectomy (central prophylactic vs. therapeutic compartment), and adjuvant medical treatment for differentiated thyroid cancer are currently debated and present unique challenges in the treatment of these patients.

2. Risk Factors

In-depth knowledge of the risk factors that may predispose to developing thyroid cancer is required when a patient is being assessed with complaints related to the thyroid gland such as thyroid nodules, voice changes, or symptoms of dyspnea, dysphagia, or sensation of suffocation. These risk factors include a personal or family history of thyroid cancer, certain diseases with a genetic predilection towards the development of thyroid cancer, and previous radiation exposure. Most thyroid cancers are idiopathic. However, the thyroid gland is very sensitive to radiation-induced oncogenesis, and radiation is the main environmental cause of thyroid cancer [15] [16] [17].

Personal history of exposure to ionizing radiation represents approximately 9% of all cases of thyroid cancer, and the risk is inversely related to the age at which the exposure was suffered, but directly related to the radiation dose, increasing linearly to a dose of 20 Gy [16] [18] [19]. Studies evaluating the effects of accident radiation exposure at the Chernobyl nuclear power plant have found a 5 to 6-fold increase in the incidence of thyroid cancer among people who lived in the Chernobyl area and were under 18 years at the time of the accident [10] [16]. When thyroid cancer develops as a result of exposure to ionizing radiation, it is invariably of the papillary type and behaves similarly to sporadic thyroid papillary cancer, although the evidence we have as a result of the Chernobyl nuclear disaster suggests that radiation dose may be related to the aggressiveness or differentiation of thyroid cancer [16]. Children exposed to the Chernobyl disaster had a higher proportion of thyroid tumors that were less well differentiated and of the papillary subtype of solid variant than patients who had no history of radiation exposure [16]. The type of radiation, along with the radiation dose, has been associated with the aggressiveness of thyroid cancer [18]. Differ-
ent forms of radiation have been linked to different genetic alterations associated with thyroid cancer, resulting in variable aggressiveness. Therefore, radiation exposure plays a critical role in the development of thyroid cancer, especially in patients younger than 15 years, and can play a role in its aggressiveness based on acquired genetic alterations and radiation dose [16] [18] [19] [20].

Having a personal history of thyroid cancer increases the risk of developing subsequent or recurrent thyroid tumors substantially. Most differentiated thyroid cancers are sporadic, and at least 5% of these patients will have family disease [21]. There is evidence of a family predisposition, with several inherited syndromes that demonstrate an increased risk of developing thyroid cancer. The mechanisms underlying these associations are not well known. Certain pathological subtypes of thyroid cancer should raise the suspicion of family syndromes that have a genetic predisposition to develop said cancer. As for example, the cribriform-morular variant of papillary thyroid cancer is associated with familial adenomatous polyposis and should raise concerns about a germline mutation of the APC gene and a predisposition to colon and rectum cancer [22]. Familial adenomatous polyposis has been associated with the development of all different subtypes of differentiated thyroid cancer [23] [24]. Families related to familial adenomatous polyposis with cases of thyroid cancer should begin surveillance/screening at age 15, or earlier if family members are affected at younger ages [22] [23] [24] [25].

The Carney complex is a rare genetic condition associated with mutations in the PRKAR1A gene that manifests with skin pigmentation, myxomas, schwannomas and thyroid abnormalities, including differentiated thyroid cancer [26]. Cowden syndrome is caused by a mutation in the PTEN germ line and is associated with the development of benign and malignant breast and thyroid lesions [27]. Peutz-Jeghers syndrome is due to germline defects in STK11 (LKB1) and is associated with gastrointestinal hamartomatous polyps, pigmented mucocutaneous lesions, and differentiated thyroid cancer [28].

During the last decade, significant advances have been made in the identification of genes related to the pathogenesis of thyroid cancer. Studies of the patterns of genetic alterations present in thyroid tumors suggest that there are differences in the pathogenesis of different types of thyroid tumors, which probably explains the variable range of biological behavior observed among thyroid cancers [29] [30] [31]. The initial event in the development of papillary thyroid cancer is usually the result of the accumulation of several mutations [30]. In approximately 50% of cases, a constitutive activation of the BRAF kinase, a member of the Ras/MAPK pathway, is present and is the result of a V600E amino acid substitution [32]. BRAF normally depends on the activation of Ras to propagate the extracellular signal transduction. In certain scenarios, activation of the Ras oncogene (found before BRAF) has also been implicated as an initiating event in papillary thyroid cancer, as well as in follicular thyroid cancer [32]. Somatic mutations have been found in the Ras oncogene in benign and malignant
thyroid tumors, and therefore appear to be an early event in thyroid tumorigenesis [30] [31]. Some studies suggest that Ras mutations are more prevalent in follicular thyroid carcinomas, in the follicular variant of papillary thyroid cancer, and in follicular adenomas [32]. Ras mutations may result in allelic loss or in chromosomal rearrangements that lead to an increase in thyroid follicular cancer formation rates [32]. Chromosomal rearrangements have also been observed in the formation of RET/PTC oncogenes and imply an unfavorable prognosis [33]. There are variable data regarding the usefulness of BRAF, TP53 and TERT mutations tests in risk stratification of patients with thyroid cancer [34] [35]. BRAF V600E mutations have been associated with worse results in papillary thyroid cancer, with higher recurrence and death rates [35].

Thyroid cancers are highly vascularized and elevated levels of vascular endothelial growth factor have been identified in these tumors, suggesting that angiogenic pathways may be a potential target for treatment [29]. In addition, during the past 30 years, thyroid cancers have been shown to be associated with genetic mutations that lead to aberrant intracellular signaling (Table 1). Preclinical and clinical data suggest that inhibition of intracellular signaling cascades, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathways may be effective in cancer treatment of thyroid [7] [33] [36] [37] [38] [39] [40]. RET kinase activation by a germline mutation is associated with the development of familial medullary thyroid cancer. Similar mutations have been detected in somatic cells that produce greater RAS/RAF activation in approximately 50% of sporadic thyroid medullary cancers [41] [42]. MAPK activation in papillary thyroid cancers can occur through RET/PTC translocations or mutations in RAS or BRAF [32]. The PI3K pathway is also activated by mutations in PAX8/PPARγ in follicular thyroid cancers [43]. This greater understanding of the mutations involved in thyroid tumorigenesis will likely lead to new systemic therapies for the treatment of advanced disease.

**Table 1.** Prevalence of mutations in different pathological subtypes of thyroid cancer.

<table>
<thead>
<tr>
<th>Type of Thyroid Cancer</th>
<th>Mutation</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Papillary</td>
<td>BRAF V600E</td>
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</tr>
<tr>
<td></td>
<td>RET/PTC</td>
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</tr>
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<td></td>
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<tr>
<td></td>
<td>RAS</td>
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<td>PI3KCA</td>
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<tr>
<td>Follicular</td>
<td>RAS</td>
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<tr>
<td></td>
<td>PAX8/PPARγ</td>
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<tr>
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<td>Medullary</td>
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<tr>
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</tbody>
</table>
The RET proto-oncogene is a tyrosine kinase receptor that is primarily expressed in tumors of neural crest/neuroectoderm origin, which explains the high incidence of these mutations in medullary thyroid carcinomas that originate in para-follicular cells (C cells) [44]. The RET gene is found on chromosome 10 and germline mutations produce activating mutations that change direction that are responsible for 95% of hereditary medullary thyroid carcinomas, including those associated with multiple endocrine neoplasia 2A (Sipple syndrome) and 2B (Wagenmann-Froboese syndrome) and familial medullary thyroid cancer [44] [45]. In 80% of cases of medullary thyroid carcinoma, the disease is sporadic, without an inherited etiology, but a somatic mutation is identified in the RET gene in 40% to 70% of these sporadic cases [41] [42]. In these sporadic cases, mutations are found most frequently in codon 918 that results in the constitutive activation of the RET tyrosine kinase receptor [46]. Almost all patients with multiple endocrine neoplasia 2A or multiple endocrine neoplasia 2B that is transmitted in an autosomal dominant manner will develop medullary thyroid cancer and the detection of germline RET gene mutations has been of great value in the early identification of patients who have a genetic basis for their disease. Even in patients with sporadic medullary thyroid cancer, 6% to 10% of these patients will have a mutation in the RET proto-oncogene germline, which reveals a new family of patients with previously undiagnosed medullary thyroid cancer [41] [42] [45]. The discovery of the RET proto-oncogene has had a significant clinical impact, which affects the scrutiny and prophylactic treatment of patients who are members of the families of patients with multiple endocrine neoplasia or with familial medullary thyroid carcinoma [47].

Anaplastic thyroid carcinoma develops from the dedifferentiation of thyroid tumors, although the specific reason for this transformation has not been well clarified. Mutations in the p53 suppressor gene are frequently found in anaplastic thyroid carcinoma and are absent in well-differentiated thyroid neoplasms [48] [49]. This observation suggests that p53 mutations play a role later in the pathogenesis of the thyroid tumor, specifically, in the transition from dedifferentiation to the anaplastic phenotype. A large number of mutations in other pathways, including the PI3K/Akt and Ras/MAPK pathways have also been implicated in the formation of ATC [48] [49].

3. Pathology

As previously mentioned papillary, follicular, oxytic, medullary, and anaplastic thyroid cancer constitute the vast majority of all thyroid tumors (90%) and the remaining proportion represents lymphoma, squamous cell carcinoma, sarcoma, melanoma or metastatic disease (breast cancer, renal cell cancer, lung cancer, colon/rectal cancer, and gastric carcinomas) [8] [50]. Papillary and follicular thyroid cancer are broadly classified as differentiated thyroid tumors but can be subclassified based on their histological appearance or biological behavior (Table 2).
Table 2. Pathological classification of malignant thyroid tumors [8] [50].

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Histologic Variants</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary (89.4%)</td>
<td>Conventional/Classic</td>
<td>65% - 85%</td>
</tr>
<tr>
<td></td>
<td>Follicular Variant</td>
<td>15% - 20%</td>
</tr>
<tr>
<td></td>
<td>Tall Cell</td>
<td>5% - 10%</td>
</tr>
<tr>
<td></td>
<td>Solid</td>
<td>1% - 3%</td>
</tr>
<tr>
<td></td>
<td>Diffuse sclerosing</td>
<td>1% - 2%</td>
</tr>
<tr>
<td></td>
<td>Papillary Micro-Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oncocytic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Columnar Cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clear Cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Morular Cribriforme</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marco-follicular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papillary with Hobnail Characteristics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papillary with stroma similar to fascitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined Papillary and Medullary Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Papillary with dedifferentiation to Anaplastic Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Follicular (4.6%)</td>
<td>Hurthle (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>Insular</td>
<td></td>
</tr>
<tr>
<td>Medullary (1.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic (0.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous Cell Carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastatic Tumors</td>
<td></td>
</tr>
</tbody>
</table>

Papillary thyroid cancer accounts for approximately, based on the most recent statistics, 89.4% of all thyroid malignancies and is the predominant histology observed in patients exposed to radiation [8] [15] [16] [17] [18]. The average age of diagnosis is between 30 and 40 years and women are affected more frequently than men (2:1 ratio) [13] [51] [52]. The macroscopic appearance of papillary thyroid cancer can be very variable. Most tumors tend to be markedly circumscribed, solid, firm, and white in color, but a significant percentage of tumors can be cystic [50]. It is not uncommon to have a solid primary tumor with cystic metastases to a lymph node [50]. Papillary thyroid cancer may have a pattern of infiltrating growth in the thyroid or may show a direct extra-thyroid extension to adjacent tissues [51] [52]. Unlike normal thyroid gland or benign thyroid lesions that protrude on sectioning, papillary thyroid cancer remains flat [53]. The diagnosis is made by microscopic evaluation and can be made on the basis of a fine needle biopsy (FNAB) [34] [53].

Conventional papillary thyroid cancer shows a papillary architecture with ramifications [51] [52]. The papillae are covered by cells with eosinophilic cytoplasm and with enlarged nuclei [50] [52]. Cell polarity may be abnormal or completely lost in some tumors [50]. It is not uncommon to have a solid primary tumor with cystic metastases to a lymph node [50]. Papillary thyroid cancer may have a pattern of infiltrating growth in the thyroid or may show a direct extra-thyroid extension to adjacent tissues [51] [52]. Unlike normal thyroid gland or benign thyroid lesions that protrude on sectioning, papillary thyroid cancer remains flat [53].
thyroid cancer [50] [51] [53]. These psamoma bodies are present in 50% of cases and help ensure the diagnosis of papillary cancer [53]. Some tumors may also contain multinucleated giant cells [50].

The definitive diagnosis is made on the basis of cellular and nuclear characteristics (cytological characteristics) with cells that adopt a cuboidal form with nuclear “grooving” and cytoplasmic inclusions [50] [51] [52] [53]. These characteristic findings are described as the pathognomonic nuclei of “Orphan Annie” [53]. Papillary cancer is characterized by multifocality in 18% to 85% of patients and is associated with an increased risk of lymph node metastasis [53]-[61]. Metastases to cervical lymph nodes are quite common in patients with papillary cancer at the time of diagnosis, with a frequency that varies between 30% to 80% in some series [53] [62] [63] [64]. Despite this high incidence, the 10-year survival rate remains 95% [8].

Follicular cancer represents the second most frequent thyroid cancer, approximately 4.6% of all thyroid cancers [8]. These tumors are most frequently found in geographic areas with iodine deficiency and, like papillary cancer, have a female predominance with a ratio of 3:1 (women/men) [8] [65] [66] [67]. Follicular cancer tends to occur in an older population compared to other differentiated thyroid tumors. Its maximum incidence is between the ages of 40 and 60, compared to the incidence of papillary cancer that reaches an earlier peak (usually 10 years less), between the ages of 30 to 50 years [53] [67]. Follicular cancer is often found in association with benign thyroid disorders, such as endemic goiter, and a relationship between chronic stimulation with thyroid stimulating hormone (TSH) and follicular carcinoma due to the increased incidence of follicular cancer has been suggested in areas with iodine deficiency [65] [66]. Patients generally present with a clinical history of a solitary thyroid nodule, which has often rapidly increased in size [53].

The histopathology of follicular tumors varies from a normal epithelium, well differentiated tumors with a follicular and colloid differentiation (findings associated with a good prognosis) to poorly differentiated tumors with solid growth, absence of follicles, marked nuclear atypia and vascular and/or capsular invasion (characteristics that are associated with a worse prognosis) [68]. Follicular tumors are usually unifocal, well encapsulated, containing highly cellular follicles, and are easily confused with benign follicular adenomas in BAAF [53]. The pathological diagnosis of this malignant neoplasm can only be made by permanent cuts, demonstrating the presence of capsular and/or vascular invasion [53].

In follicular tumors the micro-follicular architecture is uniform with a collection of cuboidal cells that cover the follicles. In addition, features compatible with papillary cancer, such as psamoma bodies and nuclear changes (such as the appearance of frosted glass, longitudinal grooves, nuclear overlap and inclusions), must be absent [50] [52] [69] [70]. Follicular thyroid tumors are classified into one of three groups according to the type and degree of invasion [68] [69] [71]:

DOI: 10.4236/ijohns.2019.86024 224 Int. J. Otolaryngology and Head & Neck Surgery
- Minimally invasive follicular thyroid cancer, which demonstrates only the invasion of the tumor capsule without vascular invasion (low-risk tumor according to the guidelines of the American Thyroid Association [ATA]) (Table 3);
- Encapsulated angioinvasive follicular thyroid cancer, which demonstrates minor vascular invasion (≤4 foci of angioinvasion within the tumor or tumor capsule) with or without capsular invasion (low-risk ATA tumor) (Table 3);
- Widely invasive follicular thyroid cancer, which is characterized by:
o  Wide invasion of the tumor capsule;
o  A multinodular tumor without a well-defined capsule that invades the normal thyroid surrounding the tumor; and/or
o  Extensive vascular invasion (>4 foci of angioinvasion) (high-risk ATA tumor) (Table 3).

Regional metastasis to cervical lymph nodes is somewhat rare in follicular cancer, being present in 5% to 13% of cases in the initial presentation [53] [72]. Distance dissemination is more common in the initial presentation compared to papillary cancer and is observed in 10% to 33% of patients, most often it presents with hematological dissemination to the lungs or bone (lytic lesions) even in those with small primary tumors, although tumors smaller than 2 cm in size have not been associated with metastatic disease [73]. The 10-year survival rates for follicular thyroid cancer are 70% to 95%, slightly worse than those for papillary cancer, possibly due to late presentation and the presence of distant metastases in the initial diagnosis.

Hürthle cell carcinoma (also known as oncocytes, or Askanasy cells), although

### Table 3. ATA risk stratification system to estimate the risk of persistent/recurrent disease.

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary thyroid cancer with all of the following:</td>
<td>Any of the following present:</td>
<td>Any of the following present:</td>
</tr>
<tr>
<td>- No local or distant metastases</td>
<td>- Microscopic invasion of peri-thyroid soft tissues</td>
<td>- Macroscopic tumor invasion</td>
</tr>
<tr>
<td>- All the macroscopic tumor has been resected (R0)</td>
<td>- Cervical ganglionic metastases or avid I-131 metastatic foci in the neck on post-treatment examination after thyroid bed ablation</td>
<td>- Incomplete tumor resection with macroscopic residual disease</td>
</tr>
<tr>
<td>- No invasion of local and regional tissues</td>
<td>- Tumor with aggressive histology or vascular invasion (aggressive histologies include high cell tumors, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, Hobnail variant)</td>
<td>- Remote metastasis</td>
</tr>
<tr>
<td>- The tumor does not have an aggressive histology (aggressive histology’s include high-cell, insular tumors, columnar cell carcinoma, Hürthle cell carcinoma, follicular thyroid cancer, Hobnail variant)</td>
<td>- Clinical N0 or ≤5 pathological micro-metastases; N1 (&lt;0.2 cm in the largest dimension)</td>
<td>- Postoperative serum thyroglobulin suggestive of distant metastases</td>
</tr>
<tr>
<td>- Without vascular invasion</td>
<td>- Well-differentiated, encapsulated intra-thyroid follicular cancer</td>
<td>- Pathological N1 with any metastatic lymph node ≥ 3 cm in the largest dimension</td>
</tr>
<tr>
<td>- There is no uptake of I-131 outside the thyroid bed in the post-treatment examination</td>
<td>- Well-differentiated intra-thyroid follicular thyroid cancer with capsular invasion and zero or minimal vascular invasion (&lt;4 foci)</td>
<td>- Follicular thyroid cancer with extensive vascular invasion (&gt;4 foci of vascular invasion)</td>
</tr>
<tr>
<td>- Clinical N0 or ≤5 pathological micro-metastases; N1 (&lt;0.2 cm in the largest dimension)</td>
<td>- Intra-thyroid, unifocal or multifocal papillary micro-carcinoma, including mutated BRAF V600E (if known)</td>
<td></td>
</tr>
<tr>
<td>- Clinical N1 or &gt;5 pathological N1 with all affected lymph nodes &lt; 3 cm in the largest dimension</td>
<td>- Multifocal papillary thyroid micro-carcinoma with extra thyroid extension and BRAF V600E mutation (if known)</td>
<td></td>
</tr>
<tr>
<td>- Follicular thyroid cancer with extensive vascular invasion</td>
<td></td>
<td></td>
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</tbody>
</table>

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considered a variant of follicular cancer, deserves a separate discussion since it comprises 2% of all thyroid neoplasms and has a biological behavior and a natural history that distinguishes them from follicular cancer [8] [53] [74]. These tumors are formed by sheets of polygonal and hyperchromatic cells that contain abundant mitochondria [74]. Hürthle tumors are characterized by the presence of a cell population of “oncocyes”, mostly eosinophilic oxyphilic cells with abundant cytoplasm, very compact mitochondria and round oval nuclei with prominent nucleoli [74]. Like follicular cancer, Hürthle carcinoma requires a definitive pathological study to identify vascular or capsular invasion [53] [72]. Unlike follicular cancer, Hürthle carcinomas are often multifocal (30%), have regional lymph node metastases (25%), and often fail to concentrate radioactive iodine [53]. In part, due to these factors, patients with Hürthle carcinoma have higher tumor recurrence rates and lower survival rates compared to patients with papillary or follicular carcinomas [53].

Medullary thyroid carcinoma is a neuroendocrine tumor of the parafollicular cells or C cells of the thyroid gland [75]. Approximately 1.7% of thyroid neoplasms are medullary carcinomas [8] [75]. Although most cases are sporadic, 15% to 25% of cases are part of an autosomal dominant hereditary syndrome [75]. Calcitonin production is a characteristic feature of this tumor [53]. C cells originate in the embryonic neural crest; As a result, medullary carcinomas often have the clinical and histological features of other neuroendocrine tumors such as carcinoid tumors and pancreatic islet cell tumors.

The sporadic form of medullary thyroid cancer typically presents as a unilateral solitary nodule (75% to 95% of patients) in the fifth decade of life [76] [77] [78] [79]. Family forms, such as multiple endocrine neoplasia (MEN 2A), multiple endocrine neoplasia (MEN 2B) and familial spinal cancer, occur in the fourth decade and are typically multifocal [76] [77] [78] [79]. Due to the embryological origin of medullary thyroid cancer (C cells), these tumors are located in the upper poles of the thyroid gland where these cells reside [53]. It is believed that the presence of C cell hyperplasia is an omen for the development of hereditary spinal cancer [53] [76] [77] [78] [79]. These tumors are not encapsulated, nor well defined, and consist of a heterogeneous mixture of fusiform or round cells [53] [76] [77] [78] [79]. The cells are separated by fibrous septa and amyloid, the latter of which helps in the diagnosis of spinal cancer by immunohistochemical staining for calcitonin and carcinoembryonic antigen [53]. Although these tumors grow slowly, they have a tendency to metastasize early, usually before the primary tumor has reached 2 cm [53].

Approximately 50% to 70% of patients with medullary thyroid cancer have clinically detectable cervical lymph node involvement at the time of diagnosis [53] [76], about 15% percent have symptoms of compression or invasion of the upper aerodigestive tract, such as dysphagia or hoarseness, and approximately 5% to 10% have distant metastatic disease [75] [80] [81]. The survival of patients with medullary thyroid cancer is between that of differentiated thyroid cancers
and undifferentiated (anaplastic) thyroid cancers. When the disease is limited to the thyroid gland, the 10-year survival rate is 90% compared to patients with distant metastatic disease that has a 10-year survival of only 20% [81].

Anaplastic thyroid tumors are undifferentiated tumors of the thyroid follicular epithelium representing less than 1% of all malignant thyroid tumors [82]. These neoplasms are highly aggressive and are considered one of the most lethal malignancies, with a mortality close to 100% [82] [83]. It is believed that these tumors arise from well differentiated thyroid tumors, but over time they suffer from dedifferentiation [81] [84]. Because activating mutations of the BRAF and RAS genes are observed in both well-differentiated thyroid malignancies and in anaplastic thyroid cancer, it is suspected that these are early events in the pathway of this disease [85]. Late events in disease progression that are most commonly seen in anaplastic cancer compared to well-differentiated tumors include mutations in the p53 tumor suppressor protein [86] [87] [88] [89], 16p [90], catenin (cadherin-associated protein), beta 1, and PIK3CA [91].

The annual incidence of anaplastic cancer is approximately one to two cases per million people and represents between 0.8% and 9.8% of all thyroid cancers worldwide [82] [92] [93] [94] [95]. Patients with anaplastic cancer are generally older at the time of diagnosis than those with differentiated cancer; The average age at diagnosis is 65 years, and less than 10% of patients are under 50 years [96] [97]. The vast majority of patients with anaplastic thyroid cancer (60% to 70%) are women [96] [97]. About 20% of patients with anaplastic thyroid cancer have a history of differentiated thyroid cancer, and 20% to 30% of patients have synchronous differentiated cancer [98] [99] [100] [101] [102]. The vast majority of synchronous thyroid tumors are papillary carcinomas but coexisting follicular tumors have also been identified. Approximately 10% of patients with Hürthle cell thyroid tumors have foci of anaplastic cancer within Hürthle cell cancer [103].

Patients with anaplastic thyroid carcinoma usually manifest clinically with a rapidly growing tumor and symptoms of dysphagia, dysphonia, or dyspnea secondary to extrinsic compression of the tumor that is often fixed to adjacent structures [53]. However, regional or distant metastases are evident at the time of diagnosis in 90% of cases [101] [103] [104] [105]. Regional extension sites may include peri-thyroid fat and pre-thyroid muscles, lymph nodes, larynx, trachea, esophagus, tonsils, large neck vessels, and the mediastinum [101]. Metastatic disease at diagnosis is found in 15% to 50% of cases [98] [99] [100] [102]. The most common site of distant metastases is the lungs (up to 90% of cases) [99] [100]. These metastases are usually massive intrapulmonary lesions, but there may be pleural involvement. About 5% to 15% of patients have bone metastases [98] [99] [100] [102]. 5% of patients have brain metastases, and some have metastases in the skin, liver, kidneys, pancreas, heart and adrenal glands [99] [100] [101] [106] [107] [108] [109] [110].

The tumor is not encapsulated and often contains areas of necrosis that may result in a non-diagnostic FANB that would lead to an incisional biopsy to en-
sure diagnosis and rule out possible lymphoma [53]. Cells are characteristically large and multinucleated with nuclear polymorphism and high mitotic activity [99]. Surgery rarely has a role in this disease; the most common procedures performed are isthmusectomy or cytoreduction to alleviate tracheal compression [81]. In rare cases that anaplastic carcinoma is diagnosed in the intrathyroid stage, without a coexisting well differentiated thyroid cancer component, thyroid lobectomy with wide margins of adjacent soft tissue on the side of the tumor is an appropriate surgical management [98]. If the anaplastic tumor is very small and completely confined to the thyroid, total thyroidectomy with complete tumor resection does not prolong survival compared to ipsilateral thyroid lobectomy and if it is associated with a higher complication rate [100] [102]. However, some experts prefer total or near total thyroidectomy with dissection of the central and lateral lymph nodes of the neck [111]. The reason for this is that differentiated thyroid cancer and anaplastic thyroid cancer often coexist, and total thyroidectomy offers a greater chance of complete resection [111]. For patients with small intra-thyroid anaplastic tumors associated with a differentiated thyroid cancer, total thyroidectomy is recommended, if complete macroscopic resection and minimal morbidity can be performed, to facilitate subsequent treatment of differentiated cancer [111].

Anaplastic thyroid cancers are extremely aggressive, with a specific mortality close to 100%. The average survival ranges from three to seven months, and the one and five year survival rates, are 20% to 35% percent and 5% to 14%, respectively [101] [102] [105] [112] [113] [114], with 90% of patients dying of the disease within 6 months of diagnosis, usually secondary to local progression [81].

Primary thyroid lymphoma is a rare diagnosis, but it should always be considered in the differential diagnosis of patients with thyroid nodules, goiter, and carcinomas, mainly because their prognosis and treatment differ substantially from other disorders. Lymphomas of the thyroid gland typically manifest in the seventh decade of life (the median and median age is between 65 and 75 years), affect women more commonly than men (with a female 4:1 predominance), and are often associated with a history of Hashimoto’s thyroiditis [115]-[120]. They represent less than 2% of all thyroid neoplasms and often present as a rapidly growing tumor with symptoms of dysphagia and dysphonia, possibly confusing the diagnosis with anaplastic thyroid carcinoma [121]. In a Danish epidemiological survey, the annual incidence rate was estimated at 2.1 cases per million people [115]. Pre-existing chronic autoimmune thyroiditis (Hashimoto’s disease) is the only known risk factor for primary thyroid lymphoma and is present in approximately half of patients [122]. Among patients with Hashimoto’s thyroiditis, the risk of thyroid lymphoma is at least 60 times higher than in patients without thyroiditis [115] [119] [120].

Thyroid lymphoma can be primary or secondary, they are almost always non-Hodgkin (B-cells), since thyroid Hodgkin lymphoma is extremely rare [115] [118] [122]. Only about 2% of extra lymph node lymphomas originate within the thy-
roid gland. Occasional cases of T lymphocyte lymphomas have been described, often in endemic areas for adult T-cell leukemia/lymphoma associated with lymphotropic virus-T (HTLV)-I [123] [124]. Sixty percent to 80% of thyroid lymphomas are diffuse large B-cells of the germinal center type [116] [117] [118] [125] [126]. The second most common subtype (about 30% of cases) is lymphoma of the extra-ganglion marginal marginal zone [32]. Other less common histological subtypes include follicular lymphomas; Small extra lymph node lymphomas have also been described [32]. Extra-lymph node marginal lymphomas of the type of mucous-associated lymphoid tissue (MALT) are generally associated with Hashimoto’s thyroiditis [127].

Histologically, the cells are monomorphic and stain positively for lymphocyte markers such as CD20 [81]. Tumors of MALT origin generally have a better prognosis and can often be treated with radiation therapy alone, rather than the multimodal therapy necessary to treat lymphomas other than MALT [81]. Survival rates for lymphoma located in the thyroid gland (stage IE) are generally favorable, with a 5-year survival rate of 75% to 85%. However, patients with diseases on both sides of the diaphragm (stage IIIE) or disseminated disease (stage IV) have a 5-year survival rate of less than 35% [53].

4. Diagnosis

Thyroid cancer is discovered incidentally in the vast majority of cases during imaging studies (computed tomography, positron emission tomography, magnetic resonance imaging or ultrasonography) performed for reasons unrelated to the thyroid. The vast majority of patients with thyroid cancer have no specific symptoms and the results of these incidentalomas will trigger a diagnostic evaluation. When patients present to a doctor with a specific symptom, it is often with the finding of a new tumor/thyroid nodule, an increase in size of a previously detected nodule, pain secondary to a nodule hemorrhage, or a lymph node palpable cervical [53]. Symptoms of dysphagia, dysphonia, or dyspnea often predict a poor prognosis since these symptoms are the result of a local invasion and are usually due to undifferentiated thyroid cancer, since differentiated tumors rarely invade surrounding structures [5].

Performing a medical history and a complete physical exam is the first step in the evaluation of a patient suspected of having thyroid cancer. Special attention should be given to personal history of radiation exposure, family history of thyroid malignancy, or thyroid cancer syndromes (Carney complex, multiple endocrine neoplasia, familial adenomatous polyposis, and Cowden syndrome). Also, ask about the symptoms of dysphagia, dysphonia or dyspnea that an invasive component may suggest. The presence of diarrhea or facial hyperemia in association with nodular thyroid disease should increase suspicion for medullary thyroid carcinoma [79]. The physical examination should focus on findings suggestive of invasion or regional metastases that may include fixation to surrounding structures, presence of tracheal deviation, or vocal cord paralysis [53]. In the ab-
sence of these findings, the presence of slightly grown lymph nodes (1 to 2 cm) together with a thyroid nodule suggests regional metastases [53] [81]. Palpable lymphadenopathy is most frequently identified along the middle and lower portion of the jugular chain. Finally, before any surgical intervention, the extent of the disease in the neck should be evaluated in anticipation of surgical positioning [53].

All patients undergoing thyroid surgery should have a preoperative evaluation of the voice as part of their preoperative physical examination. This should include the description of the patient if he has voice changes, as well as the evaluation of the voice doctor (recommendation # 40 of the American Thyroid Association [ATA]) [34]. The preoperative laryngeal examination should be performed in all patients with voice abnormalities in the preoperative period, a history of cervical or upper thoracic surgery, which puts the recurrent laryngeal or vagus nerve at risk, and in patients with known thyroid cancer with extra posterior thyroid extension or extensive central nodal metastases (ATA recommendation # 41) [34].

The prevalence of palpable thyroid nodules in the general population is approximately 5% to 7% in women and 1% in men living in parts of the world with sufficient iodine [1] [2]. In contrast, high-resolution neck and thyroid ultrasound can detect thyroid nodules in approximately 19% to 68% of randomly selected people, with higher frequencies in women and the elderly [3] [4]. The clinical importance of thyroid nodules lies in the need to rule out thyroid cancer, which occurs between 7% and 15% of cases, varying according to age, sex, radiation exposure history, family history, among other factors [5] [6].

If a thyroid nodule larger than 1 cm in any diameter is identified, a serum level of thyroid stimulating hormone (TSH) should be obtained (recommendation 2 ATA) [34]. If the TSH is low, a thyroid scan should be performed (the only indication today to perform this study) to document if the thyroid nodule is hyperfunctional ("hot", that is, the uptake of the marker is greater than the normal thyroid), isofuncionante ("warm", that is, the uptake of the marker is equal to the surrounding thyroid) or not functioning ("cold", that is, it has a lower uptake than the thyroid tissue) [128]. Because hyperfunctional thyroid nodules rarely contain malignancy, if one that corresponds to the nodule in question is found, a cytological evaluation is not necessary [34]. High serum levels of TSH, even within high ranges of normality, are associated with an increased risk of malignancy in the thyroid nodule, as well as a more advanced stage of thyroid cancer [129].

During the initial assessment of thyroid nodules, it is not recommended to routinely obtain serum thyroglobulin (Tg) (ATA recommendation 3) [34]. Serum levels of Tg may be elevated in the vast majority of thyroid diseases (benign and malignant) and is an insensitive and nonspecific test for thyroid cancer [130] [131]. The utility of serum calcitonin in the initial assessment of thyroid nodules has been evaluated in prospective non-randomized studies [132] [133].
[134][135], with mixed results, therefore, the ATA cannot recommend either for or against the measurement Routine serum calcitonin in patients with thyroid nodules (ATA recommendation 4) [34].

High-resolution neck and thyroid ultrasound should be performed in all patients suspected of having thyroid nodules, nodular goiter, or any radiographic abnormality that suggests a thyroid nodule detected incidentally in another imaging study (computed tomography or magnetic resonance imaging), or 18FDG-PET (ATA recommendation 6) [34]. Ultrasound of the neck and thyroid should evaluate the following characteristics [34]: the thyroid parenchyma (if homogeneous or heterogeneous), the size of the thyroid gland, the size, location, and ultrasonographic characteristics of any nodule, and finally the presence or absence of suspicious cervical lymph nodes in the central or lateral compartments [34][53]. Table 4 shows the characteristics that should be assessed in the high-resolution neck and thyroid ultrasound.

The ultrasonographic pattern associated with a thyroid nodule confers a risk of malignancy, and combined with the size of the nodule, guides decision making (Table 5). The ultrasound pattern of high suspicion of malignancy includes solid, hypoechoic nodules, or nodules with mixed components (solid hypoechoic and partially cystic nodule) with one or more of the following characteristics: irregular margins (infiltrative, micro-lobulated), microcalcifications, higher form than wide, calcifications at the edge of the cyst, evidence of extra thyroid extension [136][137][138].

The most accurate and cost-effective method for evaluating thyroid nodules is fine needle aspiration biopsy (FNAB) (ATA recommendation 7) [34]. Thyroid nodules with a higher probability of obtaining a non-diagnostic cytology (cystic component greater than 25% to 50%) or a sampling error (nodules difficult to palpate or located in the posterior portion of the thyroid lobe), it is preferred to perform a FNAB guided by ultrasound [139][140]. Figure 1 and Figure 2 provide

Table 4. The characteristics that should be assessed in the ultrasound [233][234].

<table>
<thead>
<tr>
<th>Node size (in three dimensions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The location (example—right upper lobe/ if anterior or posterior)</td>
</tr>
<tr>
<td>Description of the ultrasonographic characteristics of the thyroid nodule:</td>
</tr>
<tr>
<td>Composition of the nodule:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ecogenicity:</td>
</tr>
<tr>
<td>Isoechoic, hyperechoic, hypoechoic</td>
</tr>
<tr>
<td>Margins:</td>
</tr>
<tr>
<td>Regular</td>
</tr>
<tr>
<td>Irregular:</td>
</tr>
<tr>
<td>Defined as infiltrative, microlobed or spiculated</td>
</tr>
<tr>
<td>Presence and type of calcifications:</td>
</tr>
<tr>
<td>Marcocalcifications or microcalcifications</td>
</tr>
<tr>
<td>Shape:</td>
</tr>
<tr>
<td>If the nodule is taller than wide</td>
</tr>
<tr>
<td>Vascularity:</td>
</tr>
<tr>
<td>Central or peripheral</td>
</tr>
</tbody>
</table>
### Table 5. Ultrasonographic patterns of thyroid nodules, estimated risk of malignancy, and management guide for thyroid nodules with FNAB [34] [143].

<table>
<thead>
<tr>
<th>Ultrasonographic Pattern</th>
<th>Ultrasonographic Characteristics</th>
<th>Estimated Risk of Malignancy</th>
<th>Size to perform FNAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>Hypoechoic, solid nodules, or nodules with mixed components (solid and partially cystic hypoechoic nodule) with one or more of the following characteristics: irregular margins (infiltrative, microlobed), microcalcifications, taller than wide, calcifications on the edge of the cyst, evidence of extra thyroid extension</td>
<td>Greater than 70% - 90%</td>
<td>FNAB is recommended if its dimensions are equal to or greater than 1.0 cm</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Hypoechoic solid nodule with smooth (regular) margins without microcalcifications, no evidence of extra thyroid extension, and the shape is not taller than wide</td>
<td>10% al 20%</td>
<td>FNAB is recommended if its dimensions are equal to or greater than 1.0 cm</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, no microcalcification, no irregular margin, no evidence of extra thyroid extension, no taller than wide</td>
<td>5% al 10%</td>
<td>FNAB is recommended if its dimensions are equal to or greater than 1.5 cm</td>
</tr>
<tr>
<td>Very Low Risk</td>
<td>Spongiform or partially cystic nodules without any of the ultrasonographic features described in low, intermediate, or high suspicion patterns</td>
<td>Less than 3%</td>
<td>FNAB can be considered if its dimensions are equal to or greater than 2.0 cm. Observation without BAAF is also reasonable</td>
</tr>
<tr>
<td>Benign</td>
<td>Purely cystic nodules (without solid component)</td>
<td>Less than 1%</td>
<td>Do not perform FNAB</td>
</tr>
</tbody>
</table>

**Figure 1.** Algorithm for the initial evaluation and treatment of patients with thyroid nodules according to the ultrasonographic pattern.

**Figure 2.** Algorithm for the treatment of patients with thyroid nodules according to the pattern the result of the FNAB [143].
an algorithm for the initial evaluation and management of patients with thyroid nodules based on their ultrasonographic pattern and the results of the FNAB [34].

Non-diagnostic or unsatisfactory FNABs (Bethesda 1) are those that do not meet the quantitative or qualitative requirements established to say that the cytological assessment is adequate (i.e., the presence of at least six groups of well-visualized follicular cells, each group containing at least 10 well-preserved epithelial cells, preferably in a single lamella) [141] [142] [143]. When a BAAF is performed in a thyroid nodule and the initial cytology result is non-diagnostic, the BAAF should be repeated with the support of ultrasound; and if available, the cytological evaluation should be performed at the time of the FNAB (recommendation 10 of the ATA) [34] [144] [145] [146]. It has been suggested that FNAB should be repeated no earlier than three months after the initial FNAB to avoid a falsely positive interpretation due to biopsy-induced reactive changes [147]. Two recent studies have questioned the need for a waiting period of three months after the first FNAB because they found no correlation between the diagnostic performance and accuracy of the second FNAB and the waiting time between procedures [148] [149]. The ATA tells us that a waiting period of three months after a non-diagnostic biopsy is likely not necessary [34]. Thyroid nodules that have had multiple FNABs that turned out to be non-diagnostic without having a highly suspected ultrasonographic pattern may be recommended observation vs. surgical excision to have a definitive histopathological diagnosis (ATA recommendation 10) [34].

In published series of patients classified according to the Bethesda system, non-diagnostic samples constituted 2% to 16% of all FNAB samples, of which 7% to 26% were resected [150] [151] [152]. The frequency of malignancy among all FNABs initially rated as non-diagnostic was 2% to 4% and among the non-diagnostic samples that were finally resected the frequency of malignancy 9% to 32% [150] [151] [152].

If the thyroid nodule turns out to be benign in cytology after a FNAB (Bethesda 2), no additional diagnostic studies or immediate treatment are required (ATA recommendation 11) [34]. Although prospective studies are lacking, the rates of malignancy in the retrospective series range from 1% to 2% [143] [153] [154] [155].

FNAB classified as atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda 3), is characterized by having specimens containing cells with architectural and/or nuclear atypia that are more prominent than expected for benign changes, but not sufficient for be located in one of the highest risk diagnostic categories [141] [143] [156]. In the studies that used the criteria established by the Bethesda System, the risk of cancer for patients with atypical nodules of undetermined significance or follicular lesion of undetermined significance who underwent surgery was 6% to 18% if NIFT (follicular thyroid neoplasia. Non-invasive with papillary nuclear characteristics) is not
considered as cancer, and 10% to 30% if NIFT is considered as a cancer [143].

For thyroid nodules with atypical cytology of undetermined significance or follicular lesion of undetermined significance after a FNAB, with worrying clinical and ultrasonographic characteristics, the assessment can be continued by repeating the BAAF or if you have the technology you can use molecular tests to complement the risk assessment of malignancy instead of proceeding directly with either a surveillance strategy or diagnostic surgery (lobectomy) [143]. Patient preference should be considered in decision making (recommendation 15 of the ATA) [34]. If the FNAB is not repeated, and molecular tests are not performed, or both studies proved inconclusive, a diagnostic surgical excision can be performed for thyroid nodules with Bethesda 3 classification, according to clinical risk factors, ultrasound pattern and patient preference (ATA recommendation 15) [34].

The diagnostic category of the Bethesda IV, follicular neoplasm/suspected cytology of follicular neoplasm is used for cellular aspirates:

- Composed of follicular cells arranged in an altered architectural pattern characterized by cell crowding and/or microfilm formation, lacking nuclear characteristics of papillary carcinoma; or
- Compounds almost exclusively of oncocytic cells (Hurthle) [141] [143] [157] [158].

This is an intermediate risk category of malignancy in the Bethesda system, with an estimated risk of malignancy between 10% to 40% if NIFT is not considered as cancer, and between 25% to 40% if NIFT is considered as cancer [143]. This category represents 1% to 25% (average, 10%) of all FNAB samples [34].

Diagnostic surgical excision (lobectomy) is the long-established standard for the treatment of thyroid nodules with Bethesda IV cytology. However, today if the technology is taken into account, after taking into account the clinical assessment and ultrasonographic characteristics, molecular tests can be used to complement the assessment of the risk of malignancy rather than proceed directly with surgery (recommendation 16 of the ATA) [34]. Patient preference should be considered in clinical decision making. If molecular tests cannot be performed or are undetermined, surgical removal can be considered for the definitive diagnosis of thyroid nodules classified as Bethesda IV (ATA recommendation 16) [34].

The diagnostic category of the Bethesda V system, suspected cytology for malignancy represents 1% to 6% of all FNABs, and is reserved for aspirates with cytological characteristics that generate a high suspicion of malignancy (mainly for papillary thyroid carcinoma) but that they are not sufficient for a conclusive diagnosis [141] [143] [159]. This is the category with the highest risk of undetermined cytology in the Bethesda System, with an estimated cancer risk of 45% to 60% if NIFT is not considered as cancer and 50% to 75% if NIFT is considered as cancer [143]. Due to the high risk of cancer, the diagnosis of suspicious papillary carcinoma is an indication for surgery [34].
If the FNAB results in a suspicious cytology for papillary thyroid carcinoma, surgical treatment should be very similar to the management of a frankly reported FNAB. Factors that we must take into account in offering the definitive treatment with a suspicious cytology for papillary thyroid carcinoma, are the clinical risk factors, the ultrasonographic characteristics, the patient’s preference and possibly the results of the molecular tests (BRAF, RAS, RET/PTC, PAX8/PPAR) (ATA recommendation 17) [34].

If the cytological result is a diagnosis of primary thyroid malignancy, Bethesda VI, surgery is generally recommended (ATA recommendation 12) [34]. A diagnostic cytology of primary thyroid malignancy will almost always lead to thyroid surgery. However, in some parts of the world under active research protocol active surveillance can be offered as an alternative to immediate surgery in certain patients who meet some very specific criteria [160] [161]:

- Patients with very low risk tumors (for example, papillary microcarcinomas without clinically evident metastases or local invasion, and without convincing cytological evidence of aggressive disease);
- Patients with high surgical risk due to multiple comorbidities;
- Patients with a relatively short lifespan (for example, severe cardiopulmonary disease, other malignant diseases, very old age);
- Patients with concurrent medical or surgical problems that must be addressed before thyroid surgery.

5. Molecular Studies in the Valuation of Thyroid Nodes

In recent years, advances have been made in the identification of genes related to the origin of thyroid cancer (see Table 1). Studies of the patterns of genetic alterations found in thyroid tumors suggest that there are differences in the pathogenesis of different types of thyroid tumors, which probably explains the range of biological behavior observed between different types of thyroid neoplasms [81]. The genomic panorama of papillary thyroid cancer was recently described as part of The Cancer Genome Atlas (TCGA) project in which a low frequency of somatic mutations was found compared to other carcinomas and there was a dominant role and mutual exclusivity of generating genetic mutations, somatic in the MAPK and PI3K pathways [162]. In approximately 50% to 60% of cases, a constitutive activation of the BRAF kinase, a member of the Ras/MAPK pathway, is present and generally results from a substitution of amino acids V600E [32] [162]. BRAF normally depends on the activation of Ras to propagate extracellular signal transduction [30].

The TCGA work indicated that papillary thyroid tumors that have the BRAF V600E mutation represent a diverse group of tumors and should not be considered a homogeneous group; and I conclude that more studies are needed to capture their genetic diversity [162]. On certain occasions, activation of the Ras oncogene, located before BRAF, has also been implicated as an initiating event of papillary thyroid carcinoma, as well as in follicular thyroid tumors [30] [162].
Somatic mutations have been identified in the Ras oncogene (H-, K-, N-Ras) in benign and malignant thyroid tumors (in 12% of papillary thyroid carcinomas in TCGA), and therefore appear to be an early event in thyroid tumorigenesis [162]. Some studies suggest that Ras mutations are more prevalent in follicular thyroid cancers, the follicular variant of papillary thyroid cancer, and in follicular adenomas [163]. Ras mutations can result in allelic loss or in chromosomal rearrangements that lead to increased rates of thyroid follicular cancer formation [163]. There are differences in signaling in papillary thyroid tumors driven by Ras and BRAF V600E; Papillary tumors with BRAF mutations signal primarily through MAPK while papillary tumors with Ras mutations signal through MAPK and PI3K; This may have broad implications for targeted therapies [30][163].

Chromosomal rearrangements have been observed in the formation of RET/PTC fusion oncogenes; radiation-induced papillary tumors harbor this alteration [164]. There are other relatively rare oncogenic fusions described in papillary thyroid tumors such as BRAF, PAX8/PPARG, ETV6/NTRK3 and RBPMS/NTRK3 [165].

The RET proto-oncogene is a tyrosine kinase receptor that is expressed primarily in tumors of neural crest origin, which explains the high incidence of mutations in medullary thyroid cancers that originate in parafollicular cells (C cells) [166]. The RET gene is found on chromosome 10 and germline mutations result in missense activating mutations that are responsible for 95% of hereditary medullary thyroid carcinomas, including those associated with multiple endocrine neoplasia 2A and 2B [166][167]. In 80% of cases of medullary thyroid cancer, the disease is sporadic, without a hereditary etiology, but a somatic mutation is identified in the RET gene in 40% of these sporadic cases [79][81][167]. In sporadic cases, mutations are found most often in codon 918 that results in the constitutive activation of the RET tyrosine kinase receptor [75]. Almost all patients with multiple endocrine neoplasia 2A and 2B that are transmitted in an autosomal dominant manner will develop medullary thyroid cancer and the detection of germline mutations in the RET gene has been of great value in the early identification of patients who have a genetic basis for your disease [75]. Even in patients with sporadic medullary thyroid carcinoma, 6% to 10% of these patients will have a mutation in the RET proto-oncogene germ line, which reveals a new family of patients with previously undiagnosed medullary thyroid carcinoma [81]. The discovery of the RET proto-oncogene has had a very important clinical impact, which affects screening and prophylactic treatment of patients who are members of families with multiple endocrine neoplasia and relatives of medullary thyroid cancer [81]. The somatic mutation in the Ras gene is observed in approximately 15% of patients with sporadic medullary thyroid carcinoma [167].

Larger studies on the use of molecular tests in patients with undetermined BAAF respectively evaluated a panel of seven genes of genetic mutations and chromosomal reconstructions (BRAF, RAS, RET/PTC, PAX8/PPAR) [168], an expres-
sion classifier gene (GEC 167; expression of messenger RNA of 167 genes) [169], and the immunohistochemistry of galectin-3 (in cell blocks) [170]. There is currently no single optimal molecular test that can definitively confirm or rule out a malignant neoplasm in all cases of undetermined cytology, and more studies are needed long-term results that demonstrate clinical utility before the standard becomes, but the future of the evaluation of thyroid nodules and management is going in this direction.

6. Treatment of Thyroid Cancer

The treatment of thyroid tumors, and in some cases, when more tissue is needed to properly diagnose a thyroid nodule, is surgical resection. The goal of thyroid cancer management remains the complete elimination of the disease with minimal morbidity [81]. Adequate surgical treatment will allow careful postoperative follow-up, adjuvant therapies if necessary, and minimizes the possibility of disease recurrence.

Surgery for thyroid cancer is a vital element of a multifaceted treatment approach. The recommended operation must be compatible with the general management strategy and the monitoring plan recommended by the multidisciplinary team. Experienced surgeons should be referred to patients with high-risk characteristics (clinical disease N1, concern for invasion of the recurrent laryngeal nerve, or extremely invasive disease), since both the quality of the surgery and the experience of the surgeon may have a significant impact on clinical outcomes and complication rates [171] [172] [173] [174].

Because papillary thyroid cancer has an extremely low mortality rate, recurrence of the disease has become the main objective of interest when deciding on optimal surgical management for most patients [81]. For patients with papillary thyroid cancer measuring more than 1 cm, the surgery that has historically been recommended is a total thyroidectomy that certainly remains the appropriate operation for well-differentiated high-risk thyroid cancers [34]. The reasons used to consider performing a total thyroidectomy in low-risk thyroid carcinoma include lesions identified within the contralateral thyroid lobe because papillary thyroid cancer foci are found bilaterally in up to 85% of cases and in 5% to 10% of cases of recurrence the focus of recurrence is in the contralateral lobe when a thyroid lobectomy is performed [81]. From the postoperative point of view, the remaining thyroid tissue, if a more conservative resection is performed, makes radioactive iodine ablation of the remaining gland prohibitive. In addition, the measurement of serum thyroglobulin as a marker of persistent or recurrent disease after thyroid lobectomy is more difficult to interpret given the remaining thyroid tissue [81]. A total thyroidectomy avoids these difficulties and minimizes re-operative surgery that is associated with an increase in complication rates.

If surgical treatment is chosen for patients with thyroid cancer less than 1 cm without extra thyroid extension and without clinical evidence of nodal metastas-
es (cN0), the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe (ATA recommendation 35) [34]. Thyroid lobectomy is a suitable treatment for small, unifocal intra-thyroid carcinomas, in the absence of previous radiation to the head and neck, familial thyroid carcinomas, or clinically detectable cervical lymph node metastases (ATA recommendation 35) [34]. The patient’s preference should always be taken into account during the treatment discussion.

For patients with thyroid cancer greater than 1 cm and less than 4 cm without extra thyroid extension, and without clinical evidence of nodal metastases (cN0), the initial surgical procedure may be a bilateral procedure (almost total or total thyroidectomy) or a unilateral procedure (lobectomy) (ATA recommendation 35) [34]. Thyroid lobectomy may be the initial treatment for low-risk papillary and follicular carcinomas; however, the team managing the patient can choose total thyroidectomy to allow treatment with radioactive iodine or to facilitate the follow-up of these patients (ATA recommendation 35) [34]. The patient’s preference should always be taken into account during the treatment discussion.

There is controversy over whether it should be performed and the extent of prophylactic dissection of the lymph nodes in order to prevent local recurrence, provide more accurate staging, and increase survival. The distinction between a dissection of the therapeutic versus prophylactic (or elective) central compartment is that a therapeutic dissection implies that nodal disease has already occurred and has been detected clinically or by preoperative imaging (cN1 disease) [53] [81]. A dissection of the elective or prophylactic central compartment implies that there is no clinical or radiographic evidence of nodal metastases [53] [81]. This difference is important because the impact of having clinically detectable lymph nodes on survival and local recurrence may differ compared to microscopically detected disease. Similarly, a dissection of the central compartment can be ipsilateral (the same side as the dominant tumor) or bilateral (ipsilateral and contralateral) and it is important to document this distinction in the surgical note.

The central compartment (level VI) is limited superiority by the hyoid bone, inferiorly by the innominate artery, and laterally by the carotid arteries [34]. Therapeutic dissection of the central compartment (level VI of the neck) for patients with clinically involved central nodes should accompany total thyroidectomy to provide complete resection of the disease (ATA recommendation 36) [34]. Preventive/prophylactic dissection of the central compartment (ipsilateral or bilateral) in patients with papillary thyroid carcinoma with clinically non-involved lymph nodes (cN0) in patients with advanced primary tumors (T3 or T4), or clinically compromised lymph nodes in the lateral compartment of the neck (cN1b), or if the information will be used to plan additional steps in therapy (ATA recommendation 36) [34]. Thyroidectomy without prophylactic dissection of the central compartment is appropriate for small papillary tumors (T1 or T2), non-invasive, with clinically negative lymph nodes (cN0) and for most follicular cancers (ATA recommendation 36) [34]. Therapeutic dissection of the lymph nodes
in the lateral compartment should be performed in patients with metastatic lateral cervical lymphadenopathy proven by biopsy (ATA recommendation 37) [34]. The isolated removal of the affected lymph nodes, known as “berry picking,” violates the central compartment without adequately addressing the full extent of the disease and may be associated with higher rates of recurrence and morbidity in revision surgery [81].

Usually, the diagnosis of a follicular cell carcinoma or Hürthle is made after the surgical procedure, which is usually a thyroid lobectomy. In these circumstances, a total thyroidectomy is often performed in high-risk patients when it is anticipated that the patient will require adjuvant treatment with radioactive iodine, since all thyroid tissue must be removed for radioactive iodine to be effective [53] [81]. Patients who underwent a thyroid lobectomy should be offered to complete the total thyroidectomy to patients who would have recommended a bilateral thyroidectomy if the diagnosis had been available before the initial surgery (ATA recommendation 38) [34]. Therapeutic dissection of the lymph nodes in the central compartment should be included if the lymph nodes are clinically involved (ATA recommendation 38) [34]. Thyroid lobectomy alone can be considered as a sufficient management for low-risk papillary and follicular carcinomas (ATA recommendation 38) [34]. Ablation with radioactive iodine instead of completing thyroidectomy is not routinely recommended; however, it can be used to burn the remaining lobe in selected cases (ATA recommendation 38) [35].

Anaplastic carcinoma represents a unique challenge because it is rarely diagnosed in a timely manner, so surgical management is usually only offered as a palliative option [53] [81] [95]. In the rare case in which anaplastic carcinoma has been diagnosed incidentally or at the beginning of its evolution, total thyroidectomy with central compartment lymphadenectomy and ipsilateral modified radical lymphadenectomy offers the best chance of survival in the exceptional case that the tumor is intra-thyroid [91] [95] [101]. Given the aggressive nature and limited survival for patients with anaplastic carcinoma, aggressive surgical intervention involving resection of adjacent structures, such as the larynx, pharynx or esophagus, is often avoided due to the associated excessive morbidity [101]. Resection of disease that extends beyond the thyroid gland may be appropriate in highly selected individuals as part of a multimodal treatment regimen along with radiation, chemotherapy, and immunotherapy [99].

7. Staging of Thyroid Cancer

Staging of thyroid carcinoma is performed more frequently using the American Joint Committee on Cancer (AJCC) system [175]. Other staging systems validated by multiple studies have been used to predict the specific survival of thyroid cancer, including AGES (age, grade, extent, size), AMES (age, metastasis, extension, size), MACIS (metastasis, age, resection, invasion and size integrity) and EORTC (European Organization for Research and Treatment of Cancer). In
the medical literature between 1960 and 1970 several articles were published confirming that the cell of origin of thyroid cancer was crucial to discuss the prognosis of these tumors [176] [177]. The Mayo Clinic group reported its results from a population of 859 patients with papillary thyroid cancer treated at their institution between 1940 and 1970. Their results suggested that an advanced age at diagnosis, extra thyroid extension, and metastasis at a distance they were strong predictors of death. These results were replicated by several groups including that of Mazzaferri who reported similar results to those of the Mayo Clinic in a population of 576 patients with papillary thyroid cancer [178] [179].

The Mayo Clinic combined the risk factors of age, histological grade of the tumor, extent of the disease, and the size of the lesion in the AGES system to predict the risk of mortality (low risk or high risk). Subsequently, this system was improved to include resection quality by reporting the system as MACIS [180]. Cady et al. they reviewed the Lahey clinic database that included more than 800 patients treated over a period of four decades reporting very similar results introducing the AMES system that included age, distant metastasis, extra thyroid extension, and the size of the lesion by classifying patients in high risk or low risk groups for mortality [181]. A similar group of risk factors was reported by the Memorial Sloan Kettering Cancer Center group that resulted in the GAMES system (which included the histological grade) [182]. They separated patients and tumors into two groups, one high risk and the other low risk for mortality [182]. They also introduced an intermediate group for young patients with tumor risk factors of poor prognosis, or for elderly patients without tumor risk factors for poor prognosis [183]. The impact of lymph node metastases on thyroid cancer mortality is very limited, which is why it has not been included as a risk factor in most predictive mortality systems. The first works of Cady et al. they suggested that lymph node metastases had a protective effect [184], a finding that can be explained because their cohort consisted of young patients, and the association of young age with excellent survival and a higher incidence of lymph node metastases. Subsequently Hughes et al. showed that in patients younger than 45 years regional metastases were not associated with a higher mortality. However, in older patients, lymph node metastases had a significant impact on mortality [185]. From the last edition of the AJCC, nodal metastases (N) were included as part of staging in patients older than 45 years [186].

Many similar risk prediction tools have been published focusing on the risk of death from well-differentiated thyroid cancer [187]. Unfortunately, none of the staging systems, including the AJCC system, have been shown to be superior [175]. The ATA in 2009 and with its recent modifications in 2015 published guidelines for staging patients based on their risk of recurrence [34]. Again, predictive risk factors for recurrence include the quality of surgical resection, the presence of distant metastases, the presence of extra thyroid extension, and high-risk histopathological factors. None of the staging systems have a better predictive value than the other in the prediction of recurrent disease, especially
in individuals who develop thyroid cancer at an early age [175]. Unlike the previously cited staging systems that calculate the risk of death, nodal metastases do have an intermediate risk of recurrence. As almost no well-differentiated thyroid cancer patient is going to die of their disease, a staging system designed to predict the risk of recurrence rather than mortality can prove to be of greater clinical utility for modern physicians.

Staging using the AJCC system is recommended for all patients with differentiated thyroid cancer, depending on its usefulness in predicting disease mortality and its requirement for cancer registries (ATA recommendation 478) [175]. The 8th edition of the AJCC staging system modified the definitions of the primary tumor and nodal metastases (Tables 6-8) [175]. Age at the time of diagnosis is

Table 6. AJCC staging system for papillary, follicular, poorly differentiated, Hürthle cell, and anaplastic thyroid cancer [175].

| Definition of the Primary Tumor (T) |
| TX—Primary tumor cannot be evaluated |
| T0—No evidence of primary tumor |
| T1—Tumor ≥ 2 cm in the largest dimension limited to the thyroid: |
| T1a—Tumor ≤ 1 cm in the largest dimension limited to the thyroid |
| T1b—Tumor > 1 cm, but ≤ 2 cm in the largest dimension limited to the thyroid |
| T2—Tumor > 2 cm, but ≤ 4 cm in the largest dimension limited to the thyroid |
| T3—Tumor > 4 cm limited to the thyroid or extra gross thyroid extension that invades only the pre-thyroid muscles: |
| T3a—Tumor > 4 cm limited to the thyroid |
| T3b—Extra macroscopic thyroid extension that invades only pre-thyroid muscles (sternohyoid, sternothyroid, thyroid or omohyoid muscles) of a tumor of any size |
| T4—Includes extra gross thyroid extension: |
| T4a—Extra macroscopic thyroid extension that invades subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve of a tumor of any size |
| T4b—Extra macroscopic thyroid extension that invades the prevertebral fascia, or covers the carotid artery, or mediastinal vessels, of a tumor of any size |

| Definition of regional lymph nodes (N) |
| NX—Regional lymph nodes cannot be evaluated |
| N0—There is no evidence of loco-regional lymph node metastasis: |
| N0a—One or more benign lymph nodes cytologically or histologically confirmed |
| N0b—There is no radiological or clinical evidence of regional crazy lymph node metastases |
| N1—Metastasis to regional nodes: |
| N1a—Metastasis to lymph nodes of level VI or VII (pretracheal, paratracheal or prelaringeal/Delphiano or upper mediastinal). This may be a unilateral or bilateral disease. |
| N1b—Metastasis in the lateral, lateral bilateral lymph nodes, or contralateral (level I, II, III, IV or V), or retropharyngeal lymph nodes |

| Definition of distant metastasis (M) |
| M0—No distant metastasis |
| M1—Remote metastasis |
Table 7. Prognostic groups based on AJCC staging in well differentiated thyroid cancer [175].

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>&lt;55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T1</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T2</td>
<td>N0/NX</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T3a/T3b</td>
<td>Any N</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T4a</td>
<td>Any N</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>≥55 years</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>≥55 years</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVB</td>
</tr>
</tbody>
</table>

Table 8. Prognostic groups based on AJCC staging in anaplastic thyroid cancer [175].

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-T3a</td>
<td>N0/NX</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>T1-T3a</td>
<td>N1</td>
<td>MO</td>
<td>IVB</td>
</tr>
<tr>
<td>T3b</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVC</td>
</tr>
</tbody>
</table>

perhaps one of the most important predictive factors for patients with well-differentiated thyroid cancer, as evidenced by their inclusion in the AJCC manual, as well as in each of the other staging systems mentioned previously [175] [178]-[183]. It has also been shown in some studies that the male gender is an independent predictor of survival, since in these studies thyroid cancer is more aggressive in men [188] [189] [190], although this variable is not specifically included in any system of staging because. In general, the prognosis of patients with well-differentiated thyroid carcinoma is based on their age, sex, extent of disease and the size of their primary tumor. The issue of lymph node metastases and prognosis is still debated as previously mentioned in the text, since lymph node involvement predicts local recurrence but does not contribute significantly to patient survival [175]. Involvement of lymph nodes affects the classification of AJCC staging only in patients older than 55 years [175].

The AJCC staging for thyroid cancer stratifies patients in four stages according to the TNM classification, with the exception of anaplastic tumors, which are always considered stage IV [175]. Staging is based on the histology of the primary tumor and the patient’s age (for differentiated cancer), which demonstrates the importance of these parameters in survival and prognosis. The eighth edition of the AJCC staging system for differentiated thyroid cancer has been updated...
compared to previous editions as the age of diagnosis increased from 45 years to 55 years [175]. The limited extra thyroid extension was eliminated from the definition of T3 disease [175]. T3a is now a new category and refers to tumors larger than 4 cm in the largest dimension, but still limited to the thyroid gland [175]. T3b is also a new category defined as a tumor of any size with extra gross thyroid extension that invades only the pre-thyroid muscles [175]. Importantly, the definition of the central compartment was expanded to include both level VI and level VII lymph nodes [175].

Survival rates for various thyroid cancers are presented in Table 9. Although similar for stage I disease, survival for follicular thyroid cancer is slightly worse than for papillary cancer and this is probably due to the trend of hematogenous dissemination, age and the most advanced stage at the time of diagnosis [81]. Anaplastic thyroid cancer has one of the worst survival rates of all malignant neoplasms with a 1-year survival of 17% and a 5-year survival of approximately 6%, which demonstrates the aggressiveness of this disease [175]. In general, the prognosis for patients diagnosed with thyroid cancer is good with survival rates greater than 85% to 90% for most stages, probably as a result of the indolent nature of the disease.

8. Adjuvant Treatment

The objectives of adjuvant treatment include prolonging survival and reducing future recurrence of thyroid cancer. Retrospective cohort studies of patients followed postoperatively for several decades suggest that multimodal adjuvant therapy may decrease local recurrence and may improve survival [53] [81] [191] [192] [193] [194] [195]. The ATA recently created and updated the initial risk stratification system (Table 10), recommending its use for patients with differentiated thyroid cancer treated with thyroidectomy, based on its usefulness in predicting the risk of recurrence and/or persistence of disease [175]. This initial risk stratification system for well-differentiated thyroid cancer utilizes the histology,

| Table 9. Relative stage-specific survival for thyroid cancer [175]. |
|-------------------|---|---|---|---|
|                   | Stage I | Stage II | Stage III | Stage IV |
| Papillary Cancer  |          |          |           |          |
| 1 year            | 99.9%    | 100%     | 97.7%     | 77.6%    |
| 5 years           | 99.8%    | 100%     | 93.3%     | 50.7%    |
| Follicular Cancer |          |          |           |          |
| 1 year            | 99.7%    | 99.6%    | 91.1%     | 78.5%    |
| 5 years           | 99%      | 99.7%    | 71.1%     | 50.4%    |
| Medullary Cancer  |          |          |           |          |
| 1 year            | 100%     | 100%     | 96%       | 64.3%    |
| 5 years           | 100%     | 97.9%    | 81%       | 27.7%    |
| Anaplastic Cancer |          |          |           |          |
| 1 year            | N/A      | N/A      | N/A       | 18%      |
| 5 years           | N/A      | N/A      | N/A       | 6.9%     |
Table 10. ATA modified initial risk stratification system [34].

<table>
<thead>
<tr>
<th>ATA Low Risk</th>
<th>Papillary thyroid cancer (with all of the following):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Does not have local or distant metastases</td>
</tr>
<tr>
<td></td>
<td>• The entire macroscopic tumor has been resected</td>
</tr>
<tr>
<td></td>
<td>• It has no tumor invasion of loco-regional structures or tissues</td>
</tr>
<tr>
<td></td>
<td>• The tumor has no aggressive histology (high cell carcinoma, Hobnail variant, and columnar cell carcinoma)</td>
</tr>
<tr>
<td></td>
<td>• If I131 is administered, avid metastatic foci outside the thyroid bed should not be identified in the first post-treatment full-body thyroid scan</td>
</tr>
<tr>
<td></td>
<td>• Without vascular invasion</td>
</tr>
<tr>
<td></td>
<td>• cN0 or ≤5 pN1 micro-metastases (&lt;0.2 cm in the largest dimension)</td>
</tr>
</tbody>
</table>

| ATA Intermediate Risk | Papillary thyroid cancer of intra-thyroid follicular variant, encapsulated Intra-thyroid well differentiated follicular thyroid cancer with capsular invasion and no or minimal vascular invasion (<4 foci) Intra-thyroid, unifocal or multifocal papillary microcarcinoma, including mutated BRAF V600E (if known) |
|                       | Microscopic invasion of the tumor to the peri-thyroid soft tissues |
|                       | Avid metastatic foci of radioactive iodine in the neck at the first full-body scan post-treatment |
|                       | Aggressive histology (high cell carcinoma, Hobnail variant, and columnar cell carcinoma) |

| ATA High Risk | Papillary thyroid cancer with vascular invasion |
|              | cN1 or >5 pN1 with all lymph nodes affected <3 cm in greatest dimension Multifocal papillary microcarcinoma with extra thyroid extension and mutated BRAF V600E (if known) |
|              | Macroscopic invasion of peri-thyroid soft tissue tumor |
|              | Incomplete tumor resection |
|              | Distant metastasis |

The basis of adjuvant treatment for well-differentiated thyroid carcinoma is treatment with radioactive iodine (I131) and suppression of TSH [34]. The use of radioactive therapeutic ablation of the remaining thyroid tissue after thyroidectomy is well established, but the criteria for the use of this treatment vary...
between institutions. The majority (≥75%) of follicular cell thyroid carcinomas retain the ability of normal thyroid follicular cells to absorb and concentrate iodine [196]. This iodine concentration capacity is less efficient than that observed in normal thyroid glands, due to the abnormal architecture of follicular structures within cancer, it makes it difficult to organize and retain the isotope, which explains why cancers typically look as “cold” nodules in isotopic images on thyroid scintigraphy [196] [197]. However, this conserved differentiated function allows radioactive isotopes of iodine to be used both for localization and for the treatment of residual thyroid carcinoma [198] [199].

When administered orally, all iodine isotopes are rapidly and very efficiently absorbed from the proximal gastrointestinal tract, circulate transiently in the bloodstream, and are concentrated in tissues that express a functional sodium iodide transporter (NIS) [200]. The remaining isotope is filtered and excreted through the kidneys, with radiation exposure to the entire urinary tract. Tissues that actively concentrate iodide include normal and cancerous thyroid tissue, salivary gland, breast (particularly during breastfeeding), stomach, kidney, and colon [200] [201]. The absorption of iodine in normal and malignant thyroid tissue, although not in most other tissues, depends on the activity of the TSH receptor, which regulates expression and increases the activation of NIS in thyroid tissue [202]. Similarly, thyroid tissue is capable of organizing iodine to thyroglobulin, a reaction that requires at least one partially intact follicular structure [203]. Such organization increases the biological half-life of iodine, increasing the exposure of thyroid tissue to irradiation and improving cell injury and cell death induced by radiation [203].

Radioactive isotopes of iodine in clinical use (I131, I123) emit γ rays, which can be detected using an appropriate detection device (a gamma camera), allowing imaging of tissues that concentrate iodine and therefore the detection and localization of thyroid cancer metastasis or residues, after stimulation with TSH [204]. This full-body scanning technique became the pillar of postoperative surveillance of thyroid cancer in North America in the 80s and 90s, although it has been used less frequently in recent years, due to improved technology of ultrasound, cross-sectional images, and measurements of thyroglobulin that proved to be more sensitive and more specific [205]. However, the introduction of single photon emission tomography (SPECT), in particular, to more accurately locate areas of iodine concentration ensures that isotope images continue to play a useful role in the evaluation of patients with cancer of residual thyroid [206].

Although γ rays are high energy, their absorption in the tissue is low and most of these particles do not interact with the cell in which the iodine is concentrated, or with the surrounding tissue [207] [208]. Although this is optimal for imaging, because it provides good image resolution, γ rays are not particularly effective in the treatment of residual thyroid carcinoma, which instead depends on the emission of beta particles, the main particle emitted by the decomposition of the I131 but not of I123 [208]. Moderately high energy beta particles emitted by I131 have a medium length and a short path in human tissues, traveling, on
average, only 0.5 cm before interacting with the surrounding tissue [209]. The resulting ionization causes DNA damage, including single and double stranded DNA breaks [210]. This DNA lesion is detected by the cell, activating the p53 pathway, which is commonly intact in differentiated thyroid carcinoma cells [210]. Faced with minor damage to the DNA, cell repair mechanisms are activated, and usually restore the cell to its normal state, although with the potential for induction of additional mutations or chromosomal rearrangements. However, with more extensive DNA damage, activation of p53 triggers apoptosis (programmed cell death) of the affected cell [211] [212]. Because cancer cells, including in thyroid cancer, often lack efficient mechanisms to repair double-stranded DNA ruptures, there is reason to believe that residual thyroid cancer is susceptible to the effects of beta irradiation, more than the surrounding normal tissue, although there are still no in vitro or clinical data to support this hypothesis [213].

The disease status in the postoperative period (i.e. the presence or absence of persistent disease) should be considered when deciding whether additional treatment (for example, radioactive iodine, surgery or other treatment) may be needed (ATA recommendation 50) [34]. Postoperative serum thyroglobulin (during treatment with thyroid hormone or after TSH stimulation) can help assess the persistence of residual disease or thyroid and predict the possible recurrence of the disease in the future (ATA recommendation 50) [34]. Thyroglobulin should reach its nadir in 3 to 4 weeks after the operation in most patients. The optimal cut-off value of postoperative serum thyroglobulin or the state in which it should be measured (under treatment with thyroid hormones or after TSH stimulation) to guide decision-making regarding iodine administration is unknown radioactive.

Scanning of the entire body diagnosis with postoperative radioactive iodine may be useful when the extent of thyroid remnant or residual disease cannot be determined accurately from the surgical report or neck ultrasound, and when the results may alter the decision to treat with radioactive iodine or the activity of the radioactive iodine to be administered (ATA recommendation 50) [34]. The identification and location of the foci of uptake can be improved by computed tomography by concomitant single photon emission (SPECT/CT). When these studies are carried out in a diagnostic manner before starting the definitive treatment, I123 (1.5 to 3 mCi) or a low activity of I131 (1 to 3 mCi) must be performed, with the therapeutic activity optimally administered within 72 hours of the activity for diagnosis (ATA recommendation 50) [34].

Ablation of the possible thyroid remnant with radioactive iodine is not routinely recommended after thyroidectomy for patients with differentiated thyroid cancer at low risk of recurrence based on the ATA classification (ATA recommendation 51) [34]. Ablation of the possible thyroid remnant with radioactive iodine is not routinely recommended after lobectomy or total thyroidectomy in patients with unifocal papillary microcarcinoma, in the absence of other adverse features (ATA recommendation 51) [34]. Ablation of the possible thyroid rem-
nant with radioactive iodine is not routinely recommended after thyroidectomy in patients with multifocal papillary microcarcinoma in the absence of other adverse features (ATA recommendation 51) [34]. The consideration of the specific characteristics of the individual patient that could modulate the risk of recurrence, the implications of the disease follow-up and the preferences of the patient are relevant for the decision making of the RAI. Adjuvant therapy with radioactive iodine should be considered after total thyroidectomy in patients with differentiated thyroid cancer with a risk of intermediate recurrence based on the ATA classification (ATA recommendation 51) [34]. Adjuvant radioactive iodine therapy is routinely recommended after total thyroidectomy for patients with differentiated thyroid cancer with a high risk of recurrence based on the ATA classification (ATA recommendation 51) [34].

The role of molecular tests to guide the postoperative use of radioactive iodine has not yet been established; therefore, the ATA guidelines (ATA recommendation 52) [34] and the NCCN cannot recommend the use of molecular tests to guide the postoperative use of radioactive iodine at this time [34] [80].

If abstention from thyroid hormone intake (levothyroxine/T4) is planned before radioactive iodine therapy or diagnostic tests, levothyroxine should be suspended for 3 to 4 weeks. Liothyronine (T3) can be substituted for levothyroxine in the initial weeks, if it is planned to withdraw levothyroxine for 4 or more weeks, and in such circumstances, liothyronine should be withdrawn for at least 2 weeks. Serum TSH should be measured before administration of the radioisotope to assess the degree of elevation of TSH (ATA recommendation 53) [34]. In general, a TSH goal of greater than 30 mIU/L is recommended in preparation for treatment with radioactive iodine or before performing diagnostic tests, but there is uncertainty regarding the optimal level of TSH associated with the improvement in long-term results [214] [215].

In patients categorized by the classification of the ATA with low risk and intermediate risk ATA of recurrence without extensive lymph node involvement (T1-T3, N0/NX/N1a, M0), in whom the ablation of the remnant with radioactive iodine is planned or adjuvant therapy, preparation with recombinant human TSH hormone stimulation (rhTSH) is an acceptable alternative to thyroid hormone withdrawal to achieve thyroid remnant ablation, based on clinical evidence of superior short-term quality of life, the non-inferiority of the efficacy of ablation to the remnant, and multiple observational studies that suggest a non-significant difference in long-term outcomes (ATA recommendation 54) [34] [216] [217] [219]. In patients with intermediate-risk thyroid cancer based on the classification of ATA who have extensive lymph node disease (multiple clinically involved nodes) in the absence of distant metastases, preparation with rhTSH stimulation can be considered as an alternative to abstinence from Thyroid hormone before adjuvant treatment with RAI (ATA recommendation 54) [34]. In patients with high-risk thyroid cancer based on the classification of ATA with higher associated risks of disease-related mortality and morbidity, more data from controlled studies with long-term outcomes are needed before recom-
mending the preparation of rhTSH for adjuvant treatment with radioactive iodine (ATA recommendation 54) [34]. In patients with thyroid cancer at any level of risk with significant comorbidity that may prevent thyroid hormone withdrawal before radioactive iodine administration, the preparation of rhTSH should be considered. Significant comorbidity may include: 1) a significant medical or psychiatric illness that could be exacerbated acutely with hypothyroidism, which could lead to a serious adverse event; or 2) inability to establish an adequate endogenous TSH response with withdrawal from thyroid hormone (ATA recommendation 54) [34].

If the ablation of the remnant with radioactive iodine is performed after total thyroidectomy for low-risk thyroid cancer according to the classification of ATA or intermediate risk disease with lower risk characteristics (i.e. low volume central lymph node metastases without other disease known macroscopic residual or any other adverse characteristics), the administered activity of approximately 30 mCi is generally favored by the higher administered activities (ATA recommendation 55) [34]. Higher administered activities may have to be considered for patients receiving less than a total or near-total thyroidectomy in which a larger remnant is suspected or in which adjuvant therapy is desired (ATA recommendation 55) [34]. When radioactive iodine is intended as an initial adjuvant therapy to treat residual microscopic disease, activities administered above those used for ablation of the remnant of up to 150 mCi (in the absence of known distant metastases) are generally recommended. It is not clear whether the systematic use of higher administered activities (>150 mCi) in this context will reduce the recurrence of structural disease for T3 and N1 disease (ATA recommendation 56) [34].

A low iodine diet should be considered for approximately 1 to 2 weeks before the administration of radioactive iodine for patients who undergo ablation or treatment of the remnant (ATA recommendation 57) [34] [219] [220] [221]. A full-body scan (with or without SPECT/CT) is recommended after ablation or treatment of the remnant with radioactive iodine, to report disease staging and document the avidity of radioactive iodine to any structural disease (ATA recommendation 58) [34].

Patients receiving hormone replacement treatment as part of the adjuvant management of thyroid cancer are started with sodium levothyroxine at a dose between 1.8 to 2.1 μg/kg/day [222] [223]. The dose may vary between patients and is adjusted to achieve an adequate level of TSH suppression, as determined based on the risk status of the individual patient. Patients with high-risk thyroid cancer, the appropriate degree of initial TSH suppression is recommended below 0.1 mU/L (ATA recommendation 59) [34]. For patients with intermediate-risk thyroid cancer, the initial suppression of TSH is recommended around 0.1 to 0.5 mU/L (ATA recommendation 59) [34]. Low-risk patients according to the ATA classification that have had a remnant ablation and have undetectable thyroglobulin levels, TSH can be maintained at the lower end of the reference range (0.5 to 2 mU/L) while continuing with surveillance for recurrence (recommendation
59 of the ATA) [34]. This recommendation is valid for low-risk patients who have not undergone ablation of the remnant and have undetectable levels of thyroglobulin. Low-risk patients who have undergone ablation of the remnant and have detectable but low levels of thyroglobulin, TSH can be maintained at a slightly lower level than normal (0.1 to 0.5 mU/L) while continuing surveillance for recurrence (recommendation 59 of the ATA) [34]. This recommendation is valid for low-risk patients who have not undergone ablation of the remnant, even if the levels of thyroglobulin are high and monitoring for recurrence is continued (ATA recommendation 59) [34]. For low-risk patients who have undergone a hemithyroidectomy (lobectomy), TSH can be maintained in the mid-to-lower reference range (0.5 to 2 mU/L) while continuing surveillance for recurrence (recommendation 59 of the ATA) [34]. Thyroid hormone therapy may not be necessary if patients can maintain their TSH in this target range.

The role of radiotherapy as part of the initial adjuvant treatment regimen for differentiated thyroid cancer is controversial. Several retrospective series have reported that local control can be improved with external radiotherapy, specifically in patients with macroscopic residual disease after surgical resection or in patients considered to have a high risk of relapse; however, possible side effects should be considered [224] [225]. Currently, radiotherapy is most commonly used to alleviate metastatic or locally advanced disease, such as bone metastases or recurrences in the thyroid bed not suitable for additional surgical resection, or in an attempt to avoid more extensive surgery such as laryngectomy [34] [53] [81]. The ATA does not recommend routine adjuvant external radiation therapy for the neck in patients with differentiated thyroid cancer after complete surgical excision (ATA recommendation 60) [34].

In general, traditional chemotherapy has not been very effective in the treatment of thyroid carcinomas. Chemotherapy has a very limited use in the treatment of differentiated thyroid cancer and ATA does not recommend routine systemic adjuvant therapy in patients with differentiated thyroid cancer (beyond radioactive iodine therapy and TSH suppressive therapy) (ATA recommendation 61) [34]. However, chemotherapy, in combination with radiotherapy and surgery, is used more frequently to treat anaplastic cancer, for which there is a lack of effective therapies [111] [113] [226]. Intravenous bisphosphonates can be administered in patients with bone metastases [226].

In general, differentiated thyroid cancer is considered advanced (possibly requiring additional therapy) when recurrent or metastatic lesions no longer absorb radioactive iodine, or have increased in size as part of a recent treatment with radioactive iodine (refractory to radioactive iodine), or if the recommended lifetime dose of radioactive iodine (600 mCi) has been exceeded. Exceeding a lifetime dose of 600 to 1000 mCi increases the risk of pulmonary and spinal toxicity. Loss of radioactive iodine absorption is often associated with increased fluorodeoxyglucose uptake (FDG) in positron emission tomography (PET); therefore, additional sites of the disease are often detected with this imaging modality. Once the carcinoma no longer responds to treatment with radioactive iodine and is
PET positive, survival drops (2.5 to 3.5 years) [227]. There is an exception, those that have only one metabolically active focus (positive PET) that is suitable for resection or other modalities of local ablation [227] [228].

Considerable progress has been made in the management of patients with locally advanced and metastatic thyroid cancer. Several tyrosine kinase inhibitors have shown activity in this context, exploiting the vascular nature of these tumors and/or the strong association with genetic mutations that lead to aberrant intracellular signaling (Table 11). The majority (motesanib, sunitinib, sorafenib and pazopanib) target mitogen-activated protein kinase (MAPK) and angiogenic pathways [33] [36] [38] [39]. In a phase I study with 17 patients, sorafenib produced a partial response in 30% of patients, and stable disease in 41% of patients with differentiated thyroid cancer refractory to radioactive iodine [229]. In a phase III study of 417 patients (DECISION), the efficacy and safety of sorafenib against placebo were investigated in patients with progressive differentiated thyroid cancer and refractory to radioactive iodine [230]. Patients treated with sorafenib experienced significantly longer mean survival compared to the 10.8 month placebo group against 5.8 months (HR: 0.58, 95% CI 0.45 - 0.75; p < 0.0001), had a better response rate (12.2% against 0.5%; p < 0.0001), and stable disease ≥ 6 months (42% vs. 33%). Most of the adverse events related to this treatment were manageable (grade 1 or 2) and tended to occur at the beginning of treatment [231].

Based on these results, the US Food and Drug Administration (FDA) approved sorafenib for the treatment of well-differentiated locally advanced or metastatic, progressive thyroid cancer, refractory to radioactive iodine treatment. The recommended dose of sorafenib is 400 mg (two 200 mg tablets) twice daily without food (at least 1 hour before or 2 hours after a meal).

Lenvatinib is an oral tyrosine kinase inhibitor that targets VEGFR, fibroblast growth factor receptor, RET, KIT, and platelet-derived growth factor receptor

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**Table 11.** Results of clinical studies of agents targeted for differentiated thyroid cancer.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline characteristics (%)</th>
<th>N</th>
<th>Free survival without progression (median/months)</th>
<th>Partial response (%)</th>
<th>Stable disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib [235]</td>
<td>Papillary (50), medullary (18), follicular/Hurthle (25/18), anaplastic (3)</td>
<td>60</td>
<td>18.1</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Axitinib [236]</td>
<td>Well differentiated thyroid cancer (71), medullary (29)</td>
<td>41</td>
<td></td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>Motesanib [237]</td>
<td>Papillary (61), follicular/Hurthle (34)</td>
<td>93</td>
<td>10</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td>Pazopanib [238]</td>
<td>Differentiated thyroid cancer (progression in &lt;6 months)</td>
<td>37</td>
<td>12</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Selumetinib [239]</td>
<td>Papilla with or without follicular elements (100)</td>
<td>39</td>
<td>8</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>Sorafenib/temsirolimus [240]</td>
<td>Papillary (62), follicular/Hurthle (14), poorly differentiated (16), anaplastic (3)</td>
<td>37</td>
<td></td>
<td>22</td>
<td>57</td>
</tr>
<tr>
<td>Sunitinib [241]</td>
<td>Differential thyroid cancer (74%), medullary (26)</td>
<td>51</td>
<td></td>
<td>17</td>
<td>74</td>
</tr>
<tr>
<td>Vandetanib [242]</td>
<td>Papillary (40), follicular (13), poorly differentiated (47)</td>
<td>72</td>
<td>11.1</td>
<td>1</td>
<td>56</td>
</tr>
</tbody>
</table>

DOI: 10.4236/ijohns.2019.86024
(PDGFR) approved for the treatment of patients with differentiated thyroid cancer, locally advanced or metastatic, progressive, and refractory to radioactive iodine. In the phase III study called SELECT, Schlumberger et al., investigated the efficacy and safety of Lenvatinib versus placebo in patients (N = 392) with well-differentiated progressive thyroid cancer and refractory to radioactive iodine [231]. Patients treated with Lenvatinib experienced a significantly longer median free survival versus placebo 18.3 months versus 3.6 months (HR: 0.21, 99% CI: 0.14 - 0.31, p < 0.0001), as well as a significantly higher response rate (64.8% vs. 1.5; p < 0.0001). Adverse effects related to Lenvatinib of special interest with grade ≥ 3 include hypertension (42.9%), proteinuria (10%), arterial thromboembolic effects (2.7%) and venous thromboembolic effects (3.8%) [231].

Additional studies are underway to evaluate more agents targeting other pathways known to be altered in thyroid tumors, including the endothelial growth factor receptor and the AKT/phosphatidylinositol-4,5-bisphosphate 3-kinase pathways (Table 11). Some of the tyrosine kinase inhibitors are approved for use in the management of other tumors, and patients who do not have the ability to participate in a clinical study are sometimes treated with these agents outside the protocol [232].

9. Follow-Up of Patients with Thyroid Cancer

Most recurrences in patients with differentiated thyroid cancer occur within the first five years after initial treatment, but recurrences may also occur several decades later [34] [53] [81]. Patients with papillary cancer usually recur locally and regionally in the neck, while patients with follicular cancer recur more frequently in distant sites [34] [53] [81]. Spinal cancer can recur locally and regionally in the neck or at distant sites [75] [53] [81]. The most common site of distant metastases for thyroid tumors are the lungs, bones, soft tissues, brain, liver, and adrenal glands [34] [53] [81]. Pulmonary metastases are more common in young patients, while bone metastases occur more often in older patients [81].

Follow-up consultations for patients with differentiated thyroid carcinoma generally include a complete medical history, physical examination, blood tests that include thyroglobulin, TSH, and a high resolution medial and lateral neck ultrasound [81]. The complete physical examination and ultrasound of the medial and lateral neck serve to detect local recurrences in the surgical bed or regional lymph nodes in the neck [81]. Thyroglobulin values usually fall after thyroidectomy and ablation and serve as a sensitive indicator of recurrent or persistent disease. However, it is important to keep in mind that the production of thyroglobulin depends on TSH; therefore, TSH levels may affect the sensitivity of thyroglobulin measurements in the detection of recurrent disease [34] [53] [81]. It is important to remember that 25% of patients with differentiated thyroid cancer have anti-thyroglobulin antibodies, which falsely reduce serum thyroglobulin levels [81]. Thyroglobulin levels should always be interpreted in the context of the status of anti-thyroglobulin antibodies [34].
The NCCN and ATA guidelines recommend that during the initial follow-up, measure serum thyroglobulin (with the patient taking levothyroxine) six to 12 months (ATA recommendation # 62) [34] [80]. Checking thyroglobulin levels more frequently may be appropriate for patients at high risk of recurrence based on the ATA classification [34]. Patients with a low to intermediate risk ATA classification that achieve an excellent response to therapy, there is no evidence on the usefulness of continuing with subsequent thyroglobulin intakes (ATA recommendation # 62) [34]. The time interval between thyroglobulin measurements can be extended to at least every 12 to 24 months (ATA recommendation # 62) [34]. Serum TSH levels should be measured at least every 12 months in all patients receiving thyroid hormone therapy (ATA recommendation # 62) [34]. For patients with a high-risk ATA classification (regardless of treatment response) and all patients with incomplete biochemical response, an incomplete structural response, or an undetermined response should continue to measure thyroglobulin at least every 6 to 12 months for several years (ATA recommendation # 62) [34].

Patients with low to intermediate risk based on the classification of ATA who have had remnant ablation or adjuvant therapy, and a negative neck ultrasound, thyroglobulin should be measured at 6 to 18 months (with the patient taking levothyroxine) with one trial of sensitive thyroglobulin (<0.2 ng/ml) or after stimulation with TSH to verify the absence of disease (ATA recommendation # 63) [34]. It is not recommended to repeat the TSH stimulated thyroglobulin test for low to intermediate risk patients with excellent treatment response [34]. It may be considered to obtain stimulated levels of thyroglobulin in patients with an undetermined response, an incomplete biochemical response, or an incomplete structural response after additional treatments have been performed or when a spontaneous decrease in thyroglobulin levels is observed (with the patient being treated with levothyroxine) over time to reassess the response to treatment (ATA recommendation # 63) [34].

In patients who have undergone a thyroidectomy lower than the total (lobectomy) and in patients who have undergone total thyroidectomy but not ablation of the remnant with radioactive iodine it is recommended to obtain periodic levels of thyroglobulin (with the patient being treated with levothyroxine) during follow-up (ATA recommendation # 64) [34]. Although specific levels of thyroglobulin that optimally distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, increasing levels of thyroglobulin over time are suspected of a recurrence of the disease [34].

The NCCN and ATA guidelines recommend that during the initial follow-up, high resolution medial and lateral neck ultrasound is used to evaluate the surgical bed and the central and lateral cervical ganglion compartments at 6 to 12 months after surgery, and then periodically, depending on the patient’s risk for recurrent disease and the levels of thyroglobulin (ATA recommendation # 65) [34] [80]. If a positive result would change the management of patients, suspicious ultrasound lymph nodes measuring ≥8 to 10 mm in the smallest diameter...
should have a BAAF to send cytology with a thyroglobulin measurement in the lavage fluid of the needle [34]. Low-risk patients who have had remnant ablation, a negative neck ultrasound, and a low thyroglobulin (with the patient being treated with levothyroxine) that was obtained from a sensitive trial (<0.2 ng/mL) or after stimulation with TSH (thyroglobulin < 1 ng/mL) can be followed up mainly with clinical examination and non-stimulated thyroglobulin levels (ATA recommendation # 65) [34].

After the first full-body scan with post-treatment radioactive iodine (performed after remnant ablation or adjuvant therapy), low-to-intermediate risk patients with undetectable thyroglobulin (with the patient being treated with levothyroxine) without anti-antibody Thyroglobulin, and a negative neck ultrasound (excellent response to treatment) do not require full-body scans with routine radioactive iodine during follow-up (ATA recommendation # 66) [34]. Full-body scanning with radioactive iodine, after suspension of thyroid hormone or with recombinant human TSH, 6 to 12 months after adjuvant therapy with radioactive iodine may be useful in monitoring patients with high or intermediate risk of persistent or recurrent disease and should be performed with I123 or I131 of low activity (ATA recommendation # 67) [34].

The use of 18FDG-PET should be considered in patients with high-risk thyroid cancer with elevated serum thyroglobulin levels (generally > 10 ng/ml) with negative radioactive iodine studies (ATA recommendation # 68) [34].

The follow-up for patients with medullary thyroid cancer differs from that of tumors of origin of the follicular epithelium (papillary and follicular cancer). Therefore, the measurement of thyroglobulin has no role in the detection of recurrent disease in patients with spinal cancer. Instead, monitoring should consist of measuring serum levels of calcitonin and carcinoembryonic antigen in addition to routine neck ultrasound. Serum levels of calcitonin and carcinoembryonic antigen should be measured three months after surgery, and if they are not detected or are within the normal range, they should be measured every six months for a year and then every year thereafter (recommendation # 46 of the ATA) [75]. Patients with high levels of calcitonin in the postoperative period, but less than 150 pg/ml should undergo a complete physical examination and have a high resolution medial and lateral neck ultrasound (ATA recommendation # 47) [75]. If studies are negative, patients should be followed up with a medical history and physical examination, measurement of serum levels of calcitonin and carcinoembryonic antigen, and neck ultrasound every six months (ATA recommendation # 47) [75]. If serum levels of postoperative calcitonin exceed 150 pg/ml, an evaluation should be performed with imaging studies, including an ultrasound of the neck, computed tomography of the chest, magnetic resonance with contrast or computed tomography of the liver with three contrast phases, and bone scintigraphy and magnetic resonance imaging of the pelvis and axial skeleton (ATA recommendation # 48) [75]. In patients with serum levels of calcitonin and carcinoembryonic antigen detectable after a thyroidect-
omy, these markers should be measured at least every six months to determine their doubling times (ATA recommendation # 49) [75].

For patients diagnosed with MEN 2A or 2B, annual examinations should be performed to rule out the diagnosis of a pheochromocytoma (MEN 2A and MEN 2B) and hyperparathyroidism (MEN2A) [75]. Anaplastic carcinoma and lymphoma cannot be followed in the same way as patients with differentiated thyroid cancer. Normally the protocol includes a medical history, physical examination, neck ultrasound, computed tomography or additional MRI, and measurement of the carcinoembryonic antigen and LDH [81].

10. Conclusion

The striking increase in the prevalence/incidence of low-risk thyroid cancer over the last 10 to 20 years has required a re-assessment of the conventional one-size-fits-all approach to differentiated thyroid cancer. This conversion to a more individualized management of the patient with thyroid cancer has led to a much more risk-adapted approach to the diagnosis, initial therapy, adjuvant therapy, and follow-up of patients with differentiated thyroid cancer. This has necessitated a complete re-appraisal of our management approach to the likelihood of disease-specific mortality and the risk of structural/biochemical disease recurrence. During the last 10 years, there has seen significant adjustments to the AJCC/TNM staging system, the elaboration and validation of the ATA risk stratification system for prognostication of disease recurrence, and the identification and implementation of dynamic risk stratification to allow real-time, ongoing re-evaluation of risk from initial detection to final follow-up. Contemporary treatment of patients with thyroid malignancy requires a multidisciplinary approach involving an endocrinologist, a thyroid surgeon, a radiologist, and, on occasion, medical and radiation oncologists. In selected patient’s radioactive iodine therapy are usually effective for most patients with differentiated thyroid cancer resulting in excellent long-term outcomes in most cases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Single Piece Dental Implant: A Remedy for Atrophic Ridges: Review

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https://doi.org/10.4236/ijohns.2019.86025

1. Introduction

Rehabilitation the edentulous maxilla or mandible with implants has become a normal predictable treatment today but successful implant placement needs sufficient bone to be available (at least 13 - 15 mm length and 5 - 7 mm width) [1] [2]. Implant placement in severely atrophic jaws is especially challenging because of the poor quality and quantity of the future implant bed [3]. Calvarial or
iliac bone grafts, mental nerve displacement, all on four, nerve bypass and sinus lift procedures are often used to overcome the initially unfavorable anatomical and mechanical conditions [4] [5] [6]. Despite acceptable success rates, these approaches involve unpredictable degrees of morbidity at the donor and/or recipient sites [7]. Furthermore, patients are sometimes reluctant to undergo such procedures [8].

The conventional crestal implants are indicated in situations when an adequate vertical and horizontal bone must be available if not the prognosis is not good as soon as augmentation become part of the treatment plan. Augmentation procedures tend to increase the risks and costs of dental implant treatment as well as the number of necessary operations [1]. To avoid these procedures the other viable option for replacement in atrophic jaws is to change the implant design. Two very successful implant designs and protocols have been demonstrated in the past few decades for replacement in atrophic jaws which are Mini Dental Implants and Basal Implants [9].

Basal implant (single piece dental implant) also known as bicortical implant or just cortical implant is a modern implant system which utilizes the basal cortical portion of the jaw bones for retention of the dental implants which are uniquely designed to be accommodated in the basal cortical bone areas. The basal bone provides excellent quality cortical bone for retention of these unique and highly advanced implants. Because basal implant includes the application of the rules of orthopedic surgery, the basal implants are also called as “orthopaedic implant”. Dental implants when placed in this bone can also be loaded with teeth immediately. This science is already proved in orthopedic implants (Hip/Knee replacements). Once the patient is fitted with the artificial joint patient is asked to start using it immediately [10].

This article reviews literature of using basal implants and the differences that exist between basal implants and crestal implants in rehabilitation of atrophied edentulous jaws (Table 1) [11], types of basal implants, drawbacks of conventional implants, advantages disadvantages and complication of basal implants.

### Table 1. Comparison of conventional with single piece dental implants [11].

<table>
<thead>
<tr>
<th>Implants</th>
<th>Basal implant</th>
<th>KOS implant</th>
<th>Conventional implant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Used for multiple unit restoration especially in extraction socket allow placement in bone deficient in height and width.</td>
<td>Used for multiple unit restoration need adequate bone tissue, good D1/D2 bone.</td>
<td>Used for single or multiple unit restoration in adequate bone tissue.</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Cortical anchorage of thin screw implants (bicortical screws, BCS). Excellent primary stability can be obtained along the vertical surfaces of these implants with no need for corticalization only Osseoadaptation occure.</td>
<td>Screw implants of this type can result in lateral condensation of spongy areas. Implant stability is greatly increased by a mechanism that could be regarded as “corticalization” of the spongy bone.</td>
<td>Osseointegration: “the formation of a direct interface between an implant and bone, without intervening soft tissue”.</td>
</tr>
</tbody>
</table>
**Continued**

<table>
<thead>
<tr>
<th></th>
<th>Immediate loading 72 hours</th>
<th>Immediate loading 72 hours</th>
<th>Delayed loading 3 - 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic design</strong></td>
<td>Single sitting surgical procedure and very often flapless (no open surgical procedures are necessary). Implant procedures are less time consuming than that required for bridgework.</td>
<td>Single sitting surgical procedure and very often flapless (no open surgical procedures are necessary). Implant procedures are less time consuming than that required for bridgework.</td>
<td>Very often more complex surgical procedures are necessary, spread over 2 or 3 sittings in a period of 3 - 6 months (Implant placement, Healing Screw placement &amp; Abutment Placement).</td>
</tr>
<tr>
<td><strong>Implant procedure</strong></td>
<td>Very often more complex surgical procedures are necessary, spread over 2 or 3 sittings in a period of 3 - 6 months (Implant placement, Healing Screw placement &amp; Abutment Placement).</td>
<td>Complex—a wide array of instruments are required for placement of two piece implants</td>
<td></td>
</tr>
<tr>
<td><strong>Armamentarium</strong></td>
<td>Simple—the implant surgery kit is very simple with very few instruments</td>
<td>Complex—a wide array of instruments are required for placement of two piece implants</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Very cost effective</td>
<td>Very cost effective</td>
<td>Expensive</td>
</tr>
<tr>
<td><strong>From the patient point of view</strong></td>
<td>Less complex placement procedure</td>
<td>Less complex placement procedure</td>
<td>More complex placement procedure</td>
</tr>
<tr>
<td><strong>Long term maintenance</strong></td>
<td>Single piece, strength provided by implant is excellent</td>
<td>Single piece, strength provided by implant is excellent</td>
<td>Two piece some time the relation between them make problem</td>
</tr>
<tr>
<td><strong>Eligibility to patient</strong></td>
<td>Almost every one</td>
<td>Almost every one</td>
<td>No suitable for diabetic, Smoker and patient with uncontrolled periodontitis</td>
</tr>
<tr>
<td><strong>Size and design</strong></td>
<td>Wide range of size and design are available</td>
<td>Wide range of size and design are available</td>
<td>Limited range of size and design are available</td>
</tr>
<tr>
<td><strong>Bone used</strong></td>
<td>Basal bone more dense, mineralized and less prone to bone resorption</td>
<td>Basal bone more dense, mineralized and less prone to bone resorption</td>
<td>Crestal alveolar bone, bone is less quality and is more prone to resorption</td>
</tr>
<tr>
<td><strong>Additional surgery</strong></td>
<td>No need bone augmentation sins lift…</td>
<td>No need bone augmentation sins lift…</td>
<td>Most time need another additional surgery</td>
</tr>
<tr>
<td><strong>Prosthodontic procedures</strong></td>
<td>Very simple. Conventional impressions of the implants can be made just as is the case with routine bridgework. Very less chairside time.</td>
<td>Very simple. Conventional impressions of the implants can be made just as is the case with routine bridgework. Very less chairside time.</td>
<td>Requires more complex procedures and chair side time.</td>
</tr>
</tbody>
</table>

### 1.1. Rationale of Using Basal Implants

Alveolar bone (crestal bone) of the jaw less dense gradually starts getting reabsorbed and recedes once the teeth are lost. The bone which ultimately remains after regression of the alveolar bone following loss of teeth is the basal bone which lies below the alveolar bone. This basal bone is less prone to bone resorption and infections. It is highly dense, corticalized and offers excellent support to implants. The conventional implants are placed in the crestal alveolar bone which comprises of bone of less quality and is more prone to resorption. The basal bone is less prone to bone resorption because of its highly dense structure. The implants which take support from the basal bone offer excellent and long lasting solution for tooth loss. At the same time, load bearing capacities of the cortical bone are many times higher than those of the spongious bone. This rationale stems from orthopedic surgery and from the experience that cortical areas are essential, since, they are resistant to resorption [12].

### 1.2. Classification of Single Piece Dental Implant (Basal Implant) Based on Morphology [9]

There are four basic types of basal implants:
1) Screw Form
2) Disk Form
3) Plate Form
4) Other Forms:
   1) Screw Form (Figure 1)
      a) Compression Screw Design (KOS Implant)
      b) Bi-Cortical Screw Design (BCS Implant)
      c) Compression Screw + Bi-Cortical Screw Design (KOS Plus Implant)
   2) Disk Form (Figure 1)
      a) Basal Osseo-integrated Implant (BOI)
      b) Trans-Osseous Implant (TOI)
      c) Lateral Implant
   3) Plate Form
      a) BOI-BAC Implant
      b) BOI-BAC2 Implant
   4) Other Forms
      a) TPG Implant (Tuberopterygoid)
      b) ZSI Implant (Zygoma Screw)

1.3. Morphology of Basal Implant

The BOI (Basal Osseo Integrated) and BCS (Basal Cortical Screw) implant being produced today has a smooth and polished surface as it was found that polished surfaces are less prone to inflammation (mucositis, periimplantitis) than rough surfaces. The KOS and KOS Plus implants are surface treated (sand and grit blasting with subsequent acid etching), however, the implant neck is kept highly polished in KOS implant. In the KOS Plus implant, its neck and the basal cortical
screw part are kept heavily polished [13] [14] [15] (Figure 2).

**BOI (Lateral Basal Implants)** is inserted from the lateral aspect of the jaw bone and it requires minimum bone height of 3 mm and that means virtually every patient can be treated without bone grafting. Because bone grafting is avoided, risk groups, such as smokers and diabetics, can successfully receive these implants. Wide basal disk of the implant is stabilized into both facial as well as lingual strong cortices deep into the resorption and infection resistant zone (well deep from the crest) which guarantees safe load transmission and osseointegration. Its iso-elastic (flexible) design make it possible to connect its prosthesis to the firm and healthy natural teeth in selective cases which avoid the necessity of extraction of healthy teeth and also save the cost of the treatment. The neck of this implant can be bended to make multiple implant heads parallel for passive seating of the prosthesis and also to seat the prosthesis in the most suitable occlusion line. Masticatory load transmission is confined to the horizontal implant segments and, essentially, to the cortical bone structures [13].

**BCS (Screw Basal Implant)** is inserted like a conventional implant, but it transmits loads only into the opposing deep cortical bone that means virtually every patient can be treated without bone grafting. Because bone grafting is avoided, also risk groups, such as smokers and diabetics, can successfully receive these implants. Strictly cortical anchorage of the implant guarantees for safe load transmission and osseointegration. Minimal invasive implant placement (mostly without any flap and suture) the neck of this implant can be bended to make multiple implant heads parallel for passive seating of the prosthesis and also to seat the prosthesis in the most suitable occlusion line. These implants are also heavily polished and are flapless implants with a very small mucosal penetration diameter [10].

**Compressive implant (KOS)** is a single-component one piece screw type basal implants with a compression thread, it is used for multiple unit restoration with immediate loading in the upper and lower jaw, it can be used in combination
with other BCS basal implants (KOS Plus Implant) and allows flap and flapless placement. The first approach relies on the compression screw principle. Screw implants of this type can result in lateral condensation of spongy areas. Implant stability is greatly increased by a mechanism that could be regarded as “corticalization” of the spongy bone (KOS) [13].

1.4. Parts of Basal Implants (Figure 3)

The basal implants are single piece implants in which the implant and the abutment are fused into one single piece. This minimizes the failure of implants due to interface problems, the connections which exists in conventional two and three piece implants.

Surface of the implants:
- polished surface;
- stops bacteria and plaque from adhering to the implant neck or body.

Body of the Implants:
- the thin implant body is combined with wide thread turns that enhances the vascularity around the implant and increases the bone implant contact.

Neck of the Implant:
- the abutment can be bent by 15 - 25 degrees depending upon the length of the implant, provided the implant is placed in dense corticated bone;
- the polished surface protects the implant surface from bacterial attachment [1].

2. Draw Backs with Conventional Root form Implant [16]

1) Requires large amount of bone.
2) Require wider bone at crest to accommodate its neck which usually found lacking in many cases because of bone loss.

![Figure 3. Parts of single piece dental implant.](image-url)
3) Mostly require bone augmentation procedures at the time or before the implant insertion which increase the cost, surgery time, no. of surgeries and treatment span.

4) Most part of the implant is placed into the poor density spongy bone which cannot be loaded immediately—may require healing time up to 3 - 8 months.

5) Because of vital structures such as maxillary sinus and mandibular canals in the back region of jaws, these implants may require large amount of bone augmentations (sinus augmentation, block grafting, nerve repositioning), multiple surgical steps, higher cost and longer healing times.

6) Has a screw connection which may lead to future screw loosening/screw breakage problems under the prothesis.

7) Sensitive to infection—Theses implants have rough surface which is prone to collect infection once exposed to oral environment or placed at the infected region. Hence these implants cannot be placed into the infected tooth socket.

8) Being rough surface, these implants are prone to peri-implantitis.

9) Crestal bone loss—maximum stress/load comes on the bone crest which may cause crestal bone loss.

10) Wide neck diameter and rough surface of these implants require thick, keratinized and stable/non mobile gums around its neck to avoid the problems such as soft tissue.

3. Surgical Technique

Unlike conventional implants basal implants have a different surgical approach. The technique is simple and easy to execute and does not involve extensive drilling of bone thus avoiding thermal injury [13]. Throughout the surgery the mode of irrigation used is external and usually for almost any case a single pilot osteotomy with a “Pathfinder Drill” is sufficient for KOS, KOS Plus and BCS implants, the kit also consists of manual drills for a controlled osteotomy preparation [17] [18].

Basal implantologists do not advocate raising a flap for these implants as it results in a decreased blood supply and also because of the design of these implants raising a flap is pointless, another factor to be considered is the immediate loading of these implants; a sutured site is not a favorable area to receive an immediate prosthesis [13] [17] [18].

For the BOI implant the approach towards the bone is gained by raising a flap laterally and cutting into the bone with disk drills of required size in a lateral direction to form a “T” shaped osteotomy. The implant consequently is placed laterally and the flap is closed over it [19].

3.1. Indications [20]

1) All kinds of situations when several teeth are missing or have to be extracted.
2) When the procedure of 2-stage implant placement or bone augmentation has failed.
3) In cases of severe bone deficiency either horizontal or vertical.
3.2. Contraindications

1) Special Cases: Cases where bilateral equal mastication cannot be arranged, e.g. when chewing muscles or their innervations are partly missing (these cases may lead to problems under immediate load protocols).

2) Medical conditions: There are a number of medical conditions that preclude the placement of dental implants. Some of these conditions include: Recent myocardial infarction (heart attack) or cerebrovascular accident (stroke), Immunosuppression (a reduction in the efficacy of the immune system).

3) Medicines: A dentist will need a complete listing of all of the medicines and supplements that their patient takes. Drugs of concern are those utilized in the treatment of cancer, drugs that inhibit blood clotting and bisphosphonates (a class of drugs used in the treatment of osteoporosis).

3.3. Advantages of Basal Implants [20]

1) Safe load transmission in basal bone—Load transmission is deep in the infection free basal bone. In conventional root form implant, load transmission is near the area of bacterial attack. Cortical bone is resorption resistant due to higher mineralisation.

2) Less incidence of peri-implant infections—Implant surface is polished in basal implants and also the mucosal penetration diameter is less as compared to conventional dental implants.

3) Patient’s own alveolar bone is required—Basal implants require the patient’s own alveolar bone and no bone augmentations are required. All patients have sufficient basal bone horizontally even if vertically height is reduced. Also the duration of treatment is reduced as bone augmentations require certain amount of time for healing.

4) Immediate loading—Extremely good patient acceptance is obtained with basal implants as immediate loading is possible. There is no edentulous phase and immediate dentures are not required.

5) One stage procedure—Extractions and implant placement can be carried out in one appointment even if the teeth are periodontally infected.

6) Low demand for patient compliance.

3.4. Disadvantages with Basal Implants [21]

1) Compromised aesthetics with single tooth replacement.

2) Skilled surgeon with sound anatomic knowledge is important to carry out successful surgery.

3) Excess sound bone reduction in cases of good bone support.

4) A phenomenon called as overload osteolysis can be seen if load distribution is not done properly.

**BOI-BAC Implant, BOI-BAC2 Implant** [22] is onlay miniplate integrated implant marketed as BAC and BAC2 (not to be confused with their classical lateral osteotomy BOI implant) used in severely atrophied area as subperiosteal implant retaining by screws (**Figure 4**).
**Tuberopterygoid (TPG) Screws:** These implants are placed in the pterygoid bone and aid in providing additional support to the prosthesis. These are used in conjunct with Sinus Section technique and are placed at 20° - 45° in the bone and the angulation between BOI implant and TPG screw should not exceed 90° otherwise prosthesis placement becomes difficult (Figure 5).

**Zygomatic Screw Implant (ZSI):** These are zygomatic implants that are placed in the zygomatic bone and like the BCS implant these also have sharp edged cortical screws that gain bicortical support (Figure 6).

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![Figure 4. BOI-BAC implant, BOI-BAC2 implant.](image1)

![Figure 5. Pterygoid implant.](image2)

![Figure 6. Zygomatic screw implant.](image3)
4. Conclusion

Developments of basal implants had given positive hope for the patients with atrophied ridges which can be rehabilitated not only by avoiding augmentation procedures, time and cost but also by immediately loading of the prosthesis making them more confident and socialize normally. More than 90% of the available Implant system all around the world follows system of crestal implants. Advocates of Basal Implant systems call it to be a better alternative to crestal implants in terms of ability to restore almost any type of case, shortened treatment time, less chance of failure. However, the long term results are yet to be proven. The whole concept is based upon the fact that basal bone is the most stable of all the bones available for Implants and that its resorption rate is virtually nil. Also to add is the chances of failure due to infection is also greatly reduced since the Implant takes its primary retention from the site which is very far from the surgical area. Despite of the data available on their success in treating a variety of cases these implants have gained little trust among conventional implantologists, it seems further research and development and more concrete data on clinical cases are required to prove their efficacy as a replacement to conventional implants. Technique of placing basal implants definitely requires a skillful operator with a sound knowledge of anatomy. Complications are rare but can be fatal if the procedure is not performed properly.

Sources of Funding

This work is performed solely by the authors of this manuscript. Nobody else participated in preparation or financial aid of this work. We just spent extra time to collect the data and put it together in the form of research.

Ethical Approval

Here in Iraq, we do not have committees or organizations for ethical approval. Taking informed consent is the only standard ethical process within hospital permission rules because all hospitals in Iraq are teaching governmental hospitals therefore informed consent is taken before doing any procedure or publishing the information of any patient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


Surgery of the Goiter in the ENT Department of Chu Gabriel Toure: Problematic and Perspective

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Abstract

Aims: To describe the diagnostic aspects, surgical indications and post-operative complications of thyroidectomies performed in our department. Materials and method: A descriptive retrospective study that took place in the ENT Department and Cervicofacial Surgery of Gabriel TOURE University Hospital of Bamako. We did a comprehensive sampling of all goiter cases from January 2013 to December 2018. We included in the study, the records of patients of all ages and genders, admitted into the ward and scheduled for thyroidectomy (partial or total). The exclusion criteria were incomplete hospitalization records. There were a total of 139 files were retained. Results: In 60 months, 139 cases were collected out of 1720 patients hospitalized for surgery, representing a hospital prevalence of 8.08%. The average age was 46.89 years (123 women and 16 men). The socio-professional categories were dominated by housewives (68.34%). The reported functional signs were tachycardia, asthenia and other signs of dysthyroidism in 59% as well as signs of compression in 24.46%. In 72 cases or 51.80%, the patients consulted between 2 and 10 years of disease progression. Twenty patients or 14.39% had a history of familial goiter and 2 patients had a history of thyroid surgery. On physical examination the swelling was antero-cervical in 56.83% of cases. In 96 cases or 69.06% the glandular diameter was between 5 and 9 cm. In 2 cases or 1.43% we noted cervical adenopathy in the jugulo-carotid chain. Ultrasound, TSHus and fT4 were performed first-line and systematically in all our patients. Ultrasound objectified an appearance of multinodular goiter in 106 cases or 76.26%. In 60.43% of cases the patients were TI classes RADS 3, they...


Received: August 17, 2019
Accepted: November 24, 2019
Published: November 27, 2019

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were TI RADS 4A in 16 cases or 11.51%. CT scans were performed in 3 patients or 2.15% to specify the loco-regional extension, to look for possible lymph node invasion, and to compress or dipping the goiter. Surgical indication was placed in front of a multinodular goiter (GMN) in 106 cases or 76.26%, a single goiter in 11 cases or 7.9%, a single nodule greater than 3 cm in 17 cases or 12.23%, Basedow disease in 4 cases or 2.88% and a recurrence in one case 0.72%. We performed a lobo-isthmectomy in 56.11%, a total thyroidectomy in 20.14% of cases, subtotal in 20.86% of cases and total thyroidectomy with mediastinal recurrent lymph node curage and bilateral jugulocarotidien in 4 cases or 2.87%. Recurrent nerves were systematically searched and seen in all cases. Replacement therapy was indicated in all patients who underwent a total thyroidectomy. Complications recovered were 1 case of compressive hematoma, 6 cases of transient dysphonies and cough, 4 cases of definitive hypocalcemia. 1 case of recurrence, but no deaths were observed. Histopathology performed in all of our patients was dominated by vesicular and colloid adenoma. **Conclusion:** Thyroid surgery is a common surgery but not devoid of complications, the most dangerous of which remain recurrent impairment and definitive hypoparathyroidism. The experience of all surgical teams in the vasculo-nervous anatomy of the neck is the best guarantor to reduce and prevent complications.

**Keywords**

Goiter, Thyroidectomy, Recurrent Surgery

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1. Introduction

A goiter is a localized or generalized enlarged thyroid body. It is usually cervical but may have intrathoracic development by exceeding the upper opening of the chest [1]. On the radiological level goiter is when the thyroid volume measured in ultrasound is 18 ml in women, 20 ml in men [2]. Thyroid surgery has a special place in the treatment of multiple thyroid pathologies [3]. Its practical realization requires a perfect mastery of the anatomy of the cervical region. It consists of the partial or total removal of the thyroid gland. There are several varieties ranging from lobectomy to lobo-isthmectomy, isthmectomy and total thyroidectomy [4]. The haunting of the cervical surgeon is the management of cancer pathologies and the prevention of complications related to this surgery. Currently this morbidity is reduced thanks to better medical and endocrine preparation of patients as well as the use of monitoring and video surgery in the research and preservation of vasculo-nervous pedicles and glands parathyroids [4]. The purpose of our study was to evaluate the experience of the service in the surgical management of goiters and to compare the results of our study with those of the literature.

2. Materials and Method

This was a retrospective, descriptive study carried out in the ENT and Cervi-
co-facial Surgery Department of the Gabriel TOURE University Hospital in Bamako. We did a comprehensive sampling of all goiter cases from January 2013 to December 2018. Included in the study were the records of patients of all ages and genders, admitted into the ward and scheduled for thyroidectomy (partial or total). The non-inclusion criteria were incomplete hospitalization records. There were 19 of them. A total of 139 files were retained.

Variables Studied
- Socio-demographic aspects (age, gender, occupation, residence);
- Clinical aspects: goiter size, palpatory data;
- Paraclinical aspects: TIRADS classification;
- Therapeutic aspects: technique and postoperative follow-up ranging from 6 to 1 year.

3. Results

3.1. Hospital Frequency

In 60 months, 139 cases were collected out of 1720 patients hospitalized for surgery, representing a hospital prevalence of 8.08%.

3.2. Socio-Demographic Aspects

The female sex represented 123 cases or a sex ratio of 0.13. The average age was 46.89 years with extremes of 16 and 74 years (Figure 1). The socio-professional categories were in declining order women in the home (68.34%), Traders (10.80%), Workers (9.35%), Middle Managers (5.75%), Pupils/Students (3.60), Senior Executives (2.15%).

3.3. Clinical Aspects

The reported functional signs were tachycardia, asthenia and other signs of dysthyroidism in 59% as well as signs of compression in 24.46%. In 72 cases or 51.80% the patients consulted between 2 and 10 years of disease progression. Twenty patients or 14.39% had a history of familial goiter and 2 patients had a history of thyroid surgery. On physical examination the swelling was antero-cervical in 56.83% of cases. In 96 cases or 69.06% the glandular diameter was

![Figure 1. Distribution of patients by age group.](Effectifs)
between 5 and 9 cm. In 2 cases or 1.43% we found cervical adenopathy in the jugulocarotid chain.

3.4. Paraclinical Aspects

Ultrasound, TSHus and fT4 were performed first-line and systematically in all of our patients. Ultrasound objectified an appearance of multinodular goiter in 106 cases or 76.26%. In 60.43% of cases the patients were RADS 3 TI classes, they were TI RADS 4A in 16 cases or 11.51% and in 2 cases or 1.43% they were RADS 4B TI classes. CT scans were performed in 3 patients, or 2.15% to specify the loco-regional extension, to look for possible lymph node invasion, and to compress or dipping the goiter. The hormonal check-up carried out systematically in all our patients found euthyroidism in 43 cases or 30.9%, hyperthyroidism in 96 cases or 69.06%, zero cases of hypothyroidism. Hormonal treatment after advice from the endocrinology department has been initiated in all patients with hyperthyroidism.

3.5. Therapeutic Appearance

Surgical indication was placed in front of a multinodular goiter (GMN) in 106 cases or 76.26%, a single goiter in 11 cases or 7.9%, a single nodule greater than 3 cm in 17 cases or 12.23%, Basedow disease in 4 cases or 2.88% and a recurrence in one case is 0.72% (Table 1). We performed a lobo-isthmectomy in 56.11%, a total thyroidectomy in 20.14% of cases, a subtotal thyroidectomy in 20.86% of cases and total thyroidectomy with mediastino-recurrent lymph node cure and jugulocarotidien bilaterally in 4 cases or 2.87% (Table 2). Recurrent nerves were systematically searched and seen in all cases. Replacement therapy was indicated in all patients who underwent a total thyroidectomy. Complications recovered were 1 case of compressive hematoma, 6 cases of transient dysphonias and cough, 4 cases of definitive hypocalcemia. 1 case of recurrence, but no deaths were observed (Table 3).

3.6. Histological Aspect

For all the files studied, the anatomopathology results concluded cancer in 3 cases: 2.16% (2 cases of vesicular carcinomas and 1 case of undifferentiated carcinoma), Ridel’s thyroiditis in one case and the rest was dominated by vesicular and colloid adenoma (Table 4).

Table 1. Distribution of patients according to the indication for surgery.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Effective</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple goiter</td>
<td>11</td>
<td>7.91</td>
</tr>
<tr>
<td><strong>Multinodular goiter</strong></td>
<td><strong>106</strong></td>
<td><strong>76.26</strong></td>
</tr>
<tr>
<td>Single nodule &gt; 3 cm</td>
<td>17</td>
<td>12.23</td>
</tr>
<tr>
<td>Basedow disease</td>
<td>4</td>
<td>2.88</td>
</tr>
<tr>
<td>Recidivism</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>100</td>
</tr>
</tbody>
</table>

DOI: 10.4236/ijohns.2019.86026

Int. J. Otolaryngology and Head & Neck Surgery
Table 2. Distribution of patients according to the operative technique.

<table>
<thead>
<tr>
<th>Chirurgical method</th>
<th>Effective</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobo-isthmectomy</td>
<td>78</td>
<td>56.11</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>29</td>
<td>20.86</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>28</td>
<td>20.14</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>4</td>
<td>2.87</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3. Distribution of patients according to postoperative incidents.

<table>
<thead>
<tr>
<th>Complication and postoperative evolution</th>
<th>Effective</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compressif hematoma</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4</td>
<td>2.87</td>
</tr>
<tr>
<td>Nothing</td>
<td>127</td>
<td>91.37</td>
</tr>
<tr>
<td>Dysphonia and transient cough</td>
<td>6</td>
<td>4.32</td>
</tr>
<tr>
<td>Recidivism</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 4. Distribution of patients according to pathological findings.

<table>
<thead>
<tr>
<th>Different histological type</th>
<th>Effective</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroiditis of Ridel</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Vesicular adenoma</td>
<td>37</td>
<td>26.62</td>
</tr>
<tr>
<td>Colloid adenoma</td>
<td>53</td>
<td>38.13</td>
</tr>
<tr>
<td>Vesiculo-colloid adenoma</td>
<td>31</td>
<td>22.30</td>
</tr>
<tr>
<td>Cyst</td>
<td>14</td>
<td>10.07</td>
</tr>
<tr>
<td>Vesicular carcinoma</td>
<td>2</td>
<td>1.44</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td>Total</td>
<td>139</td>
<td>100</td>
</tr>
</tbody>
</table>

4. Discussion

4.1. Methodological Aspects

We conducted a retrospective and descriptive study on the surgical management of goiters in the ENT Department of the Gabriel TOURE University Hospital. It lasted for 5 years (January 2013 to December 2018). Retrospectiveness has given a number of limitations to our study.

- Poor preservation of archives;
- Lack of reliable and usable data in some files during the retrospective phase;
- The change of address of patients or contact persons in Bamako Failure to meet appointments for post-operative control by some patients;
- The medium- and long-term post-operative follow-up survey was conducted using hospital record often supplemented by home visits. The phone was used
to reach patients who are outside Bamako.

4.2. Hospital Frequency Aspect

In 5 years we performed 139 thyroidectomies, or 8.08% of all surgeries in the ward (n - 1720). African studies on the subject have found frequencies significantly higher than our series [5] [6]. This weakness in our hospital frequency could be explained by the fact that this surgery is also practiced in the various departments of visceral surgery.

4.3. Socio-Demographic Aspects

The average age of our patients was 46.89 years, which is no different statistically from that of African authors such as Ouedrago [7] in Burkina Faso, Dia DG [8] in Senegal, who were 46 years old, and 40 years respectively. In general the average age in thyroid pathology varies between 40 and 60 years [7] [9], so it is the prerogative of the young adult subject. In our study we noted a female predominance in 88.4%. This same observation has been corroborated by the literature [3] [7] [9]. Female predominance appears to show only that from puberty, which is explained by the intervention of hormonal factors, the presence of estrogen receptors on the vesicular cells whose growth they promote. In addition, estrogens reduce the activity of the iodine symporter and contribute to the depletion of thyroid iodine content. Pregnancy promotes the onset or development of goiters, due to hyperestrogenengineering, thyreostimulant activity of placental HCG, supply of iodine and hormones to the fetus, and finally to increased renal clearance of iodine [10].

4.4. Clinical Aspects

The consultation period varies from different studies to less than 10 years. In our series more than half of the patients had a disease progression period between 2 - 10 years. This is similar to that of some authors [5] [7]. Goiter remains asymptomatic for a long time, which does not motivate consultation very early. There are also social beliefs that patients only consult when swelling becomes very troublesome by its volume or when signs of complications and compression appear or in the face of signs of dysthyroidism. The most common reason for consultation is low anterior cervical swelling. Sometimes signs of compression or signs of dysthyroidism can be noted [7] [11]. In our study the reported functional signs were tachycardia, asthenia and other signs of dysthyroidism in 59% as well as signs of compression in 24.46%.

4.5. Paraclinical Aspects

Ultrasound was routinely performed in all of our patients. This is the reference test for thyroid nodule analysis, and for the detection of subclinical nodules (1 - 3 mm). Ultrasound criteria for suspicion of malignancy have been established. Recent studies have shown that several criteria taken in isolation have no formal
value; in contrast, the association of several traits with a proven predictive value with the diagnosis of cancer [11]. In our study, data from cervical ultrasound reports identified 2 suspicious nodules CLASSEs TI-RADS 4b whose histology concluded to carcinomas. CT scans allow a detailed morphological study of the intrathoracic portion of the goiter that is inaccessible to ultrasound. It will specify the lower and posterior limits of the goiter, its relationship with large thoracic cervico vessels and with the oeso-tracheal axis [9] [12]. In our study it was carried out in 5 suspected cases of plunging goiter and confirmed the delipping character in the mediatin associated with deviation of the tracheal axis.

4.6. Therapeutic Aspect

Surgical techniques are related to surgical indications. So our surgical indications were multi nodular goiters with or without compression, Basedow disease, single goiters and single nodules greater than 3 cm for which we practiced either a total thyroidectomy or an isthmolobectomy. These same indications have been reported by the authors [4] [5]. Today the majority of authors prefer total thyroidectomy for the surgical treatment of toxic multi nodular goiters with hormone therapy [5] [13].

4.7. Surgical Suites

In the surgical suites, the incidence of postoperative bleeding ranges from 0% to 6.5%. Male sex, the presence of cancer, the importance of the gesture, and the surgeon’s experience seem to be favourable factors [7] [14]. Prevention involves preoperative control of possible dysthyroidism, intraoperative hemostasis control, and Valsalva manoeuvre to be performed in accordance with the anaesthetist, and postoperatively by early resumption of antihypertensive treatments. In our series we noted it in one case (0.7%) requiring an opening of the thyroid lodge with drainage of the hematoma and hemostasis of the vessel responsible. The incidence of recurrent, unial or bilateral impairment during a thyroidectomy is low but not zero. The risk of recurrent paralysis is present regardless of thyroid gesture. These include the type of surgery [9], the underlying thyropa-thy, the extent of the exeresis, and the volume of activity of the surgeon. The risk is increased by the presence of cancer that imposes central curage or invades adjacent structures. Other factors were mentioned: cervical hyperextension, which stretches the nerve, the number of branches dividing the recurrent, the size of the recurrent. The prevention of recurrent paralysis is both pre- and intraoperative. Neuromonitoring (NIM) used in thyroid surgery for ten years by some teams, has been developed as an aid to the intraoperative identification of the nerve, and to the elucidation of the mechanisms involved in recurrent paralysis [9] [15]. We do not have NIM in our technical tray, but the objective is the effective acquisition in a short time to further minimize the risk of recurrent injury. In our study, recurrent lesions were 2.8% transient and transient. In the literature the rate of recurrent injury varies between 0.5% and 3.5% [14] [15].

The risk of postoperative hypocalcemia, transient or permanent, is increased
by several factors: venous drainage of parathyroids, which is done exclusively to the thyroid for the upper parathyroids; the situation under capsular frequents in cases of large goiter or more rarely the intrathyroid situation of parathyroids, most often lower, not detectable in operative. The rate of involuntary parathyroidectomy varies from 6% to 21% depending on the authors, causing transient hypocalcemia in 50% of cases, with a risk of definitive hypocalcemia in about 2% [16] [17] [18]. In our study 4 cases (2.87%) transient hypocalcemias have been observed and treated with calcium associated with vitamin D.

4.8. Anatomopathological Aspect

Histopathology can find all aspects of transition between simple hyperplasia, adenoma, differentiated cancer and anaplastic cancer. For all the files studied, we found to the results that it was a benign pathology in 97.84% and 3 cases of malignant tumors or 2.16%. Its results are comparable to those of some authors [5] [8].

5. Conclusion

Thyroid pathology has been the subject of numerous studies, but it still poses a public health problem due to the large number of outbreaks of goitreuse endemics. Thyroid surgery is a common surgery but not devoid of complications, the most dangerous of which remain recurrent impairment and definitive hypoparathyroidism. The experience of all surgical teams in the vasculo-nerve anatomy of the neck is the best guarantor to reduce and prevent complications.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


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International Journal of Otolaryngology and Head & Neck Surgery

ISSN 2168-5452 (Print)  ISSN 2168-5460 (Online)
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