Introduction to focused series on recent challenges in the management of thyroid tumors

More than half of adults have at least one thyroid nodule; most of them are benign, but cancer may occur in up to 5%. The widespread dissemination of ultrasound diagnostics and better access to healthcare services lead to detection of small, subclinical nodules and small papillary thyroid cancers. Overdiagnosis and overtreatment have been proven to result in wasteful healthcare spending, including tests and interventions which have uncertain benefit to patients survival. To counteract this phenomenon Ito *et al*. introduced active surveillance of low-risk papillary thyroid microcarcinomas (PTMCs) since 1993 at Kuma Hospital (Kobe, Japan); this option has been adopted increasingly, especially after the publication of the 2015 guidelines by the American Thyroid Association (ATA). The data collected at Kuma Hospital indicate that at the 10-year observations, the incidence of enlargement ≥3 mm was only 8% and the novel appearance of node metastasis was 3.8%. None of the patients showed distant metastasis or died of thyroid carcinoma. A portion of the patients underwent conversion surgery for various reasons, including disease progression, but no patients showed life-threatening recurrence/metastasis or died of thyroid carcinoma not only when they underwent active surveillance but also after they received conversion surgery. In contrast to clinical papillary thyroid carcinoma (PTC), PTMCs of elderly patients were less progressive than those of middle-aged and young patients, indicating that elderly patients are ideal candidates for active surveillance (1).

Although there is general support in the United States of America among physicians who treat low-risk PTC with active surveillance approach, there is reluctance to offer it because of the lack of robust evidence, guidelines, and protocols (2). In Europe, as pointed out by Czarniecka *et al*. (3) several important aspects must be additionally taken into account. These aspects include a higher prevalence of multinodular goiter and thyroiditis in the European population compared to American and Asian populations, differences in the organization and financing of healthcare systems, various aspects of legal regulations and a more conservative approach to the methods of treatment of malignancies among both patients and medical teams. However, awareness of European patients has currently increased with raising interest in active surveillance, percutaneous thermal ablative techniques or minimally invasive surgery as managements option for low-risk PTMC. However, it ought to be conducted only by experienced centers as part of clinical programs (3).

The treatment of thyroid malignancy in pregnancy remains a challenge for physicians and requires a multi-disciplinary approach, including obstetricians, endocrinologists, endocrine surgeons, nuclear medicine specialists and pediatricians. Wojtczak *et al*. (4) presented current approach to management of thyroid malignancies in pregnancy. The standardized treatment for differentiated thyroid cancer (DTC) including thyroidectomy followed by radioactive iodine (RAI) ablation poses a significant risk for both the mother and the fetus; and in most cases it can be delayed until post-partum without any negative impact on either maternal or fetal outcomes. If surgical treatment is necessary during pregnancy due to aggressive thyroid malignancy, the optimal time for surgery is the second trimester. RAI therapy, however, is contraindicated during pregnancy. The outcomes of DTC in pregnancy do not usually differ from the rest of the population with thyroid malignancy (4).

Staubitz *et al*. (5) summarized current management of follicular thyroid carcinoma (FTC). This disease entity comprises a heterogenous group of tumors, which divides into subtypes with different malignant potential: minimally invasive (excellent prognosis), encapsulated angioinvasive and widely invasive FTC (higher risk metastasis and recurrence). Numerous clinical risk factors (presence of metastases, advanced patient age, tumor size and others), which can be used to assess FTC aggressiveness, are discussed with regard to the present literature. The definitive characterization of follicular neoplasms depends on postoperative histology, due to the incapability of preoperative imaging, fine-needle aspiration cytology or molecular analysis to clearly distinguish between FTC and benign follicular thyroid adenoma. Guidelines for management of FTC (according to the WHO 2017 classification of endocrine neoplasms) are developed by the leading expert scientific societies like American Thyroid Association (ATA), British Thyroid Association (BTA), German Society of Endocrine Surgery (CAEK) and European Society of Endocrine Surgery (ESES). Hemithyroidectomy is sufficient in low-risk FTC (capsular invasion only). Thyroidectomy with postoperative radioiodine therapy is recommended for high-risk FTCs (angioinvasion; widely invasive histology). Prophylactic lymphadenectomy is not necessary. Considering clinical risk factors, an individual tailored surgical approach should be chosen, following a stepwise, escalating surgical management with restricted primary

resection (hemithyroidectomy) and, if necessary, completion surgery based on the definitive histopathology (5).

Torresan *et al*. (6) provided a comprehensive review of current approach to diagnosis and treatment of medullary thyroid carcinoma (MTC), focusing on biochemical and imaging diagnostic tools, preoperative work-up, treatment and prophylactic surgery for hereditary variants. MTC is a rare malignancy arising from parafollicular C-cells and accounts for 3–10% of all thyroid malignancies. MTC occurs mostly as a sporadic disease, but in at least 30% of cases is hereditary, caused by *RET* germline mutations. In this setting, different germline *RET* mutations lead to distinct clinical phenotypes of hereditary MTC such as familial MTC and multiple endocrine neoplasia 2A and 2B. *RET* genetic screening should be performed in all new discovered cases of MTC since about 4–10% of patients with apparently sporadic MTC have *RET* germline mutations and therefore an inheritable disease. Calcitonin (CT) is the most reliable marker of MTC for both diagnosis and follow-up after thyroidectomy. In sporadic MTC, a routine determination of CT in patients with nodular goiter has been correlated to early detection of MTC. Surgery is the only curative treatment. Since the relatively high risk of multifocal and bilateral disease and the early spread to cervical lymph nodes, total thyroidectomy and central neck lymph node dissection is the standard initial treatment. Lateral neck lymph node dissection might be considered according to imaging results and CT levels. The potential benefit of neck reiterative surgery for persistent or recurrent MTC should be balanced against the increased surgical morbidity in a scarred operative field. The treatment of locally advanced MTC that is not amenable to surgery or metastatic MTC benefits of tyrosine kinase inhibitors that have shown some effects on disease progression. External radiotherapy and cytotoxic chemotherapy have demonstrated little benefit. Prognosis strictly depends on stage of disease at diagnosis, with lower survival and cure rate for stage IV disease (6).

Konturek *et al*. (7) provided an up to date review of metastatic tumors to the thyroid gland. In general, metastases to the thyroid gland account for 1.5–3% (approximately 2%) of all malignancies, with their autopsy-confirmed incidence rate ranging from 1.25% to 24.2%. Clinical material predominantly demonstrates metachronous metastases of clear cell carcinoma of the kidney, autopsy results show a predominance of metastases of the lung, colon and breast cancers. Metastases to the thyroid gland are most commonly unifocal metachronous tumors. Multifocal synchronous tumors are associated with a considerably poorer prognosis. The diagnostic method of choice is ultrasound-guided fine needle aspiration biopsy (FNAB) combined with immunohistochemical tests. Total thyroidectomy allows for a thorough evaluation of local tumor grade and is an important factor in oncological completeness of the surgical procedure. The role of multidisciplinary team is essential because balancing between the features of the primary tumor, status of the health (patient's comorbidities), age of the patient, clinical grade, histological structure and profile of metastases at the time of diagnosis are important factors influencing individualized survival rate (7).

Russell *et al*. (8) provided a solid insight into contemporary utilization of intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) in surgery for thyroid cancer. Especially treatment of recurrent thyroid cancer may be challenging when it comes to the reoperation as it entails dissection through scar tissue and distorted anatomy. Careful preoperative evaluation is imperative for assessing risk of RLN invasion and has important bearing on patient counseling and informed consent. Whereas anatomic identification of the RLN remains key, IONM adds a functional level of neural assessment. Understanding the dynamics of loss of signal (LOS) is important for determining surgical strategy, especially as it relates to staging of bilateral surgery and avoidance of bilateral vocal cord paralysis (VCP). Neuromonitoring information incorporated with knowledge of preoperative vocal cord function, patient-specific disease information, and surgical findings informs intraoperative decision-making as it relates to management of the invaded RLN. Additionally, IONM plays an important role in mapping and identification of RLN in the settings of revision surgery complicated by scar tissue and distorted anatomy. Optimized application of IONM requires knowledge of appropriate set-up and technique so that errors associated with equipment problems can be avoided. IONM guided decision-making allows to optimize both functional and oncologic benefit which is hardly available with solely visual inspection of the nerve (8).

Graves *et al*. (9) delivered a comprehensive review on fluorescent technologies for intraoperative parathyroid identification. Parathyroid fluorescence has emerged as a useful adjunct for the detection and preservation of parathyroid glands during both thyroid and parathyroid surgery. When viewed under near-infrared light, parathyroid tissue has autofluorescent properties, which can be used to identify the parathyroid glands and distinguish them from the surrounding cervical tissues, including lymph nodes, thyroid, and fat. This near-infrared autofluorescence (NIRAF) is based on intrinsic fluorophores within parathyroid tissue and does not evaluate tissue viability. However, the addition of an intravascular fluorescent contrast,

such as indocyanine green, can help evaluate gland perfusion. These techniques are safe, require no radiation, and can be easily integrated into the surgical workflow. Though long-term clinical outcomes data, including improvement of post-thyroidectomy hypoparathyroidism and cure of hyperparathyroidism using parathyroid NIRAF and contrast-enhanced parathyroid fluorescence is currently lacking; a possible role of these techniques in improving parathyroid identification and preservation during cervical surgery and training is discussed. In this article, Graves *et al*. described the techniques of probe-based and image-based detection of parathyroid NIRAF, as well as contrast-enhanced parathyroid fluorescence. They explored the current literature surrounding these modalities, discuss advantages and limitations of the various techniques, and provide practical guidance for their use and integration into surgical practice (9).

The progress in the field of minimally invasive surgery over the last twenty years has led to the application of natural orifice transluminal endoscopic surgery for thyroidectomy and parathyroidectomy via oral incisions. The true scarless nature of this approach had fascinated the early pioneers to prove the feasibility in the field of endocrine surgery. Banuchi *et al*. (10) focused on benefits and risks of transoral endoscopic thyroidectomy via vestibular approach (TOETVA) which is the latest described remote access approach to surgery of the central neck. The unique benefit of TOETVA is that it is completely scarless as incisions are made in the vestibule of the oral cavity. Since the publication of the first case series in 2016, the number of cases has exponentially grown. Multiple studies have documented the morbidity and quality of life impact of having a visible transcervical scar. In addition, the recent literature has reported increased quality of life with TOETVA as well as improved cosmesis when compared to the traditional open approach and other remote access approaches. These benefits have led to the rapid initial adoption of TOETVA by surgeons, in contrast to slower uptakes seen with the other popular remote access approaches. Currently TOETVA is being performed internationally. A literature review of TOETVA outcomes is presented in this focused series including reported complication rates which seem to be similar to standard open thyroidectomy, with low rates of novel complications such as mental nerve injury (MNI) and carbon dioxide embolism. TOETVA should be considered a safe approach to thyroid surgery as it provides excellent cosmesis while demonstrating non-inferiority in terms of risk to the patient (RLN injury, bleeding, infection, hypoparathyroidism). Larger prospective studies should be done in the future to compare TOETVA to traditional thyroidectomy in terms of quality of life, voice outcomes and oncologic equivalency (10).

Through many trials and errors, the transoral thyroidectomy has now passed its experimental stage and is continually gaining momentum in obtaining worldwide popularity. However, the approach is yet to acquire status of the primary method of choice and therefore surgeons need to gain more evidence to standardize and popularize the approach. Lee *et al*. (11) in their article reviewed the history, indications and contraindications, technical aspects of preserving the RLN and parathyroid glands, pros and cons regarding endoscopic or robotic approach, limitations and recent advancements in the field of transoral thyroidectomy (11).

Pace-Asciak *et al*. (12) provided a surgical perspective on radiofrequency ablation (RFA) of thyroid neoplasms. RFA is a safe and effective, minimally invasive procedure that has been used for decades to treat various tumors in the body. More recently, RFA has been applied to the head and neck, namely the thyroid. Part of its appeal is the lack of a cervical incision, general anesthetic, or removal of the thyroid gland at all, making it an easy office procedure for ablation of benign or malignant tumors. For enlarged benign tumors causing compressive symptoms, RFA can provide a safe option without enduring potential hypothyroidism, or the downtown associated with surgical recovery. For autonomously functioning thyroid nodules (AFTN), RFA may produce some results for improving symptoms of hyperthyroidism as well as compression, thus expanding the existing options of radioactive iodine (RAI) and anti-thyroidal medications. For the treatment of primary or recurrent thyroid cancer, surgery is the standard of care. However, not all patients are eligible for surgery and in certain instances, revision thyroid surgery for recurrent cancer can pose significant risk to the patient. Thus, the option of a minimally invasive nonsurgical technique for ablation can improve their quality of life and provide clinicians with an extra tool in their armamentarium. Pace-Asciak *et al*. reviewed the literature of this novel procedure and the role RFA can play in treating benign tumors (nonfunctioning and functioning), primary and recurrent thyroid cancers for patients that do not wish to have surgery or are ineligible (12).

With the development of the Bethesda Thyroid Cytopathology Reporting System (TBSRTC), some of the leading problems related to the reporting of thyroid FNA samples and communication between clinicians and cytopathologists have been resolved. The TBSRTC categorizes thyroid FNAB reports under six headings, including three indeterminate categories.

The TBSRTC has brought molecular testing into use as an ancillary diagnostic tool for the FNAB cytology, allowing to avoid unnecessary surgery. Performing surgery in low- and middle-income countries has the potential to lead to unwarranted damage and interruptions to the healthcare system. Clinical risk evaluation tools and algorithms must be incorporated into the clinical practice to ensure the personalized management of indeterminate thyroid tumors. The international guidelines for the management of thyroid nodules and cancers usually cannot be used when healthcare resource are limited. As pointed out by Makay *et al*. (13) healthcare resources play an important role in indeterminate thyroid tumor management. Western countries, which have access to more advanced healthcare resources, make faster diagnostic surgery decisions than Asian countries when encountering indeterminate nodules. From an economic perspective, when faced with limited healthcare resources, surgery should not be considered as a diagnostic procedure for indeterminate thyroid tumors (13).

To sum up, in this focused series we are pleased to present a wide variety of papers addressing the most current management dilemma for thyroid tumors. Individualized approach tailored to disease and patient's expectations and balanced by estimable risks should warrant personalized management including diversity of options: observation, ablation, and scarless or conventional surgery. There is no size that fits all and hence the current management of thyroid tumors requires flexibility in addressing patient wishes. However, safety issues should remain of utmost importance and novel technologies like IONM or near-infrared detection of parathyroid glands may further improve safety minimizing risk of treatment-related morbidity.

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