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Thyroid Cancer: The Evolution of Treatment Options

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1. Introduction

Joseph Stalin once said that one death is a tragedy but a million deaths is a statistic. Medical textbooks present percentages and p values, but medical professionals must deal with one death at a time. Textbooks are read in preparation for the profession. The purpose of this chapter is to bridge the gap by presenting an historical overview of the various controversies in the field of thyroid cancer that shaped our current knowledge and thereby assist the student in grasping the underlying structure beneath the vast amount of sometimes conflicting data.

A student new to the arena may be surprised at finding the candy box assortment of colorful characters engaged in lively debate within the outwardly staid community. These people are passionate about the arcane details of thyroid carcinoma, a narrow specialty about which most students of medicine are indifferent. But the history of this field is fraught with debate, controversy, confrontations and a legacy of brave souls who dared to fight against the tide.

The current opinions, as of 2011, regarding the treatment of differentiated thyroid cancer can roughly be divided into two groups, those that aggressively promote the adoption of total thyroidectomy with radioiodine ablation followed by periodic screening for biochemical recurrence and those that do not. The latter group usually prefers to perform thyroid lobectomy when the gross tumor is small and limited to one lobe of the thyroid, which would automatically rule out post-surgical ablation and the use of recombinant-TSH to screen for thyroglobulin. The option of lobectomy, although still resisted by many in the field, was finally adopted in the 2009 version of the guideline for the treatment of differentiated thyroid carcinoma by the American Thyroid Association[1], but only for tumors measuring 10 millimeters or less. The following year, Sonkar et al[2] wrote an article titled "Papillary Thyroid Carcinoma: Debate at Rest" writing that "the controversy regarding the extent of thyroidectomy in papillary thyroid carcinoma is relatively settled" with total thyroidectomy and radioiodine ablation being the preferred option for all but the smallest tumors. This announcement, however, proved premature. The 2010 version of the Japanese guideline for the treatment of thyroid tumors declared that papillary carcinomas as large as 30 millimeters were candidates for lobectomy when they were limited to one lobe of the thyroid with little or no extra-capsular invasion and gross lymph node involvement[3]. As

for papillary carcinoma less than 10 millimeters, some Japanese surgeons are proposing that observation without surgery may be sufficient[4]. The journey that lead to this schism and how it relates to the current therapeutic options is explained in this chapter as well as the most likely course that future therapy may take.

2. The maverick

Thyroid surgery was a dangerous endeavor in the 19th century and the French Academy of Medicine officially condemned the practice, but with the introduction of anesthesia, antisepsis techniques and hemostatic forceps, the prognosis improved dramatically. Billroth reported a mortality rate of 40% early in his career which fell to 8% in the 1870s[5]. Kocher reported a reduction in mortality from 12.6% to 0.2% from the 1870s to the end of the 19th century[6]. Successful thyroidectomy lead to the discovery of postoperative hypothyroidism which in turn elucidated the true function of the normal thyroid gland[7]. Klein reported on loss of voice due to injury to the recurrent laryngeal nerves during the removal of goiter[8]. Tetany was observed in patients who underwent total thyroidectomy, but it was only with the concerted efforts of multiple investigators around the turn of the century that damage to the parathyroid glands was found to be responsible for this condition[9]. Eventually, these discoveries lead to the reduction of surgical complications in thyroid surgery.

Medical progress has advanced on a precarious balance between the pressing need for immediate solutions and the effort to keep harmful options out of the field. Pioneers of medicine made courageous, sometimes reckless, forays into uncharted territory to which we owe our current technology. But once the frontier was conquered and patient survival improved, more attention was paid to the tradeoffs of treatment, such as compromised quality of life, and efforts were made to diminish them. Surgery in particular has progressed, over the past half century, in the direction of reducing the extent of dissection and thereby lowering the risk of complications.

George "Barney" Crile Jr. stands out as the man who set the field of surgery onto this course. Father of the celebrated journalist George Crile III and son of the venerated founding member of the Cleveland Clinic, George Crile Sr., he is something of an unsung hero of modern surgery. Surgery for thyroid carcinoma of his time, called the "block dissection" or "conventional radical neck dissection", usually sacrificed the sternocleidomastoid muscle, often the accessory nerve and sometimes the inframandibular branch of the facial nerve. He wrote in 1957 "The deformities and dysfunctions which ensue are tragic consequences to teen-age girls and young women who are most commonly affected by papillary cancers of the thyroid. Loss of contour of the neck, paralysis of the muscles of the lower face, shoulder drop, later arthritic changes in the shoulder girdle, hoarseness from unilateral laryngeal nerve injuries, stridor from bilateral injuries, and tetany are serious and often permanent complications. The surgeon who inflicts them must be prepared to defend his position by incontrovertible proof of a higher rate of cure."[10] He argued that there was none. He was one of the first surgeons ever to promote the idea that "the less surgery the better", and he campaigned vigorously for the abandonment of the classic block dissection. His ideas on thyroid cancer surgery, and later breast cancer surgery, were reluctantly but steadily adopted by the surgical community and have since shaped the evolution of surgical treatment.

It would be easier to compose a narrative if the history of thyroid surgery were a linear progression from "conventional radical neck dissection" to less and less invasive procedures. But the story is more muddled, partly due to the particular characteristics of the organ and also due to entrenched positions of opinionated surgeons and oncologists. The trajectory was also confounded by the periodic infusion of breathtaking new technology for which there was widespread but misguided enthusiasm. There was no consensus for the optimum surgical procedure for thyroid cancer surgery in the early to mid-twentieth century. If the gross tumor was limited to one lobe, some surgeons performed lobectomy, some lobectomy with isthmus, some lobectomy with isthmus and a part of the opposing lobe and some insisted on total thyroidectomy. A few even dared to perform partial lobectomy and preserved most of the thyroid. The extent of lymph node dissection also varied greatly[11]. Early on, metastasis to the lymph nodes in the neck were mistaken for embryological migration error termed "lateral aberrant thyroid" and believed not to require surgery. Conventional radical dissection may have been a backlash against this initial complacency[12].

During the time Crile was battling conventional radical dissection, others were arguing for more radical surgery. Clark et al performed serial sections of the whole thyroid. He found intraglandular dissemination in 58% of the 79 cases he studied[13]. Similar studies by Black et al found multicentricity in 20%[14], and Underwood et al found contralateral lobe involvement in 32% of cases studied[15]. Each of these authors advocated total thyroidectomy or more based on their findings. However, Tollefsen, citing these works and others, compared them to the actual clinical recurrence rate in the opposite lobe. He pointed out that his recurrence rate was 3.7% and even Black, a proponent of radical surgery, had reported a recurrence in the opposite lobe in only 7%. In his 1963 report, Tollefsen wrote "The final importance of these histologic observations must rest in the clinical results. All but a small percentage of our patients have remained well for periods up to twenty-five years without clinical recurrence in the remaining lobe. We must, therefore, interpret these histologic cancers in the other lobe as being of slight importance and somewhat analogous to the autopsy incidence of microscopic cancer in the prostate."[16] It is surprising today to find that a surgeon in New York had already outlined the position taken by Japanese specialists of the twenty-first century half a century previously. Nobody today questions that papillary thyroid carcinoma is very often multi-focal, although some authors argue that microscopic multifocal disease is clinically irrelevant.

3. Stratifications

Care should be taken in reading, and especially in citing, medical reports of this era. Histologic classification and diagnosis did not follow the same criteria as we use today. Statistics were rudimentary and rarely employed anything more sophisticated than simple percentages. Most troublesome of all, such variables as the initial size of the pre-operative tumor or the age of the patient were not taken into account when discussing the merits of one surgical procedure over another. In 1953, Crile reported that patients aged over 40 at initial diagnosis had a poorer prognosis compared to patients aged under 40. He concluded "Since almost all cancers of the thyroid that occur in patients under 40 years of age are of the lowest grade malignancy, the prognosis in this age group is almost universally good if an adequate operation is performed"[17]. In his 1964 report Tollefsen analyzed 70 fatal cases of

papillary thyroid carcinoma and isolated age, initial size of tumor over 5 centimeters, recurrent laryngeal nerve palsy and distant metastasis as indicators of poor prognosis[18]. This was the beginning of the study of risk profiles in thyroid cancer. It was only after the prognostic indicators were clearly identified, and the outcome of treatment was compared among groups with equivalent risk profiles that the debate on surgical procedures rested on firm footing. Statistical techniques such as multivariate analysis were not employed in the study of thyroid cancer until the introduction of practical personal computers in the mid 1980s. Nonetheless, "conventional radical neck dissection" fell out of favor by the early 1970s.

Meanwhile, a remarkable paradigm shift was surrounding the realm of thyroid surgery. The increasing acceptance of iodine prophylaxis markedly decreased the incidence of endemic goiter. Radioiodine and anti-thyroid drugs reduced the number of surgically treated Graves disease. Prior to the development of oral steroid medications, even subacute thyroiditis was often treated by surgery, but this method was completely abandoned. The practice of irradiating children for benign diseases, which apparently increased the incidence of radiation induced thyroid cancer, was no longer performed[19]. Core needle and fine needle biopsies made preoperative differentiation of benign and malignant tumors possible. Due to these developments and others, the number of thyroid operations performed in the Cleveland Clinic fell from 2,700 in the year 1927 to less than 50 in the late 1960s[20]. Thyroid cancer effectively became the last bastion of thyroid surgery.

Imaging modalities also influenced surgery. In the late 1940s, ultrasonography was developed simultaneously in the United States, United Kingdom, Sweden and Japan. Although the earliest machines were cumbersome and impractical, the technology eventually improved to incorporate hand held probes which produced acceptably clear images. Fine needle aspiration biopsy was developed in the 1950s and eventually came into wide acceptance. But the combination of the two did not appear until the 1970s and was not widely used in the diagnosis of thyroid diseases until the 1980s. Computerized axial tomography was commercialized in the mid 1970s and magnetic resonance imaging in the early 80s, but neither machines were initially suitable for the examination of the neck area , CAT scan because of image artifacts from the bones and MRI (then called NMR-CT) because of low resolution. Both imaging technologies developed rapidly and became indispensable tools in the examination of the thyroid by the 1990s. The introduction of these diagnostic tools contributed greatly in the early detection of thyroid cancer and the incidence of thyroid cancer steadily increased[21] while the size of tumor upon discovery steadily decreased after the mid 1980s[3].

Over the years, improvements in anesthesia made it safer for surgeons to take the time to carefully visualize the recurrent laryngeal nerve which was eventually proven to diminish the incidence of paralysis[22]. The same was true for the parathyroid, which when better preserved caused fewer cases of tetany. This meant that total thyroidectomy could be performed with smaller risk of surgical complications.

So if the tumors were smaller but the complications were fewer, was it more logical to perform more conservative surgery or more radical surgery? Although this was not the question that was openly verbalized, this was the general area where the battle lines were drawn. And the debate was closely linked to the question of radioiodine therapy.

The use of radioactive isotope of iodine as a tracer for the thyroid was developed during the 1930s and 40s. Eventually, this lead to the treatment of hyperthyroidism using 131-I[23]. The experimental application of radioiodine on thyroid cancer began almost simultaneously[24]. It was soon established that replacement thyroid hormones should be withdrawn for the duration of this therapy and that healthy thyroid tissues need to be removed for this method to be effective. The use of thyroglobulin to screen for cancer recurrence was developed later[25]. It was then established that thyroglobulin measurements yield no useful information in the follow up of thyroid cancer patients in the presence of residual thyroid tissue[26]. Thus a new rationale for total thyroidectomy was introduced. Thyroid cancer patients would hence forth be given total thyroidectomy not because tumors were found in both lobes, but because it facilitated post-operative screening for recurrence and the treatment of recurrence should any be found. And not only were the thyroid removed surgically, but they were completely eradicated by means of "remnant ablation" using 131-I.

Although some surgeons were initially skeptical about the utility of radioiodine therapy in the treatment of metastatic thyroid carcinoma, the contrarians were eventually silenced as data mounted supporting its efficacy. By the 1970s few argued against the adoption of radioiodine therapy, and consequently total thyroidectomy, on patients with proven distant metastasis. Routine remnant ablation and thyroglobulin screening, however, was a different matter. Once again, superiority of one regimen over the other was frequently argued without stratifying the cases according to various risk factors. In one example, Snyder pointed out in 1983 that the actual effectiveness of routine remnant ablation in reducing morbidity and mortality was not objectively proven due to this reason[27]. In a subsequent issue of the same journal, Riccabona published a letter to the editor which included a survival curve comparing the survival of patients who had undergone radioiodine ablation and patients who had not to show that radioiodine ablation indeed had a positive effect[28]. To this, Snyder replied that this was "yet another testimonial to what has plagued the evaluation of different approaches to the treatment of thyroid cancer patients" and asked "Were Dr. Riccabona's patients randomized as to treatment? Were variables such as age, sex, histological type, histological grade, extent of disease, extent of surgery, and use of thyroid suppression therapy taken into account? What method was used in the detection of postoperative functioning tissue? Was ablation aimed at presumably normal thyroid tissue, or known residual thyroid cancer in the thyroid bed, or extrathyroidal functioning metastasis? Were these variables considered in the survival curve presented?" Few such dialogues were preserved in print, but similar debates occurred frequently in conferences around the world, occasionally accompanied by thunderous arguments and animated gesticulations, throughout the 1980s. Although not entirely as a consequence of such confrontations, the TNM staging system was introduced in 1987, AMES system in 1988, AGES system in 1987 and MACIS system in 1993.

4. Debates

Randomized prospective trials, had they been performed, may have helped settle many of the disputes. But differentiated thyroid carcinoma is an indolent cancer with a low rate of recurrence regardless of the treatment modality and often remains dormant for many years before tangible physical recurrence can be observed. This means that large numbers of patients would have to be followed for a very long time before a definite conclusion could

be reached. Thus, the studies on the optimum treatment for thyroid cancer would be left in the hands of prolific surgeons who would showcase their vast surgical experience in retrospective studies involving large numbers of patients. The field of thyroid cancer is littered with retrospective studies of hundreds, sometimes thousands of cases aimed at demonstrating the validity or otherwise of a given procedure. The extent of surgery is one of many controversial subjects that are so studied and there is a number of retrospective studies, properly stratified with AGES, AMES and pTNM, which demonstrate that total or near-total thyroidectomy reduces recurrence rates compared to lobectomy and similar unilateral resections[29)30)31)]. What is often left unsaid is that patients who undergo near-total or total thyroidectomy must receive oral hormone replacement for a lifetime, while the majority of patients who undergo unilateral lobectomy remain euthyroid without medication. As a consequence, the patients who undergo lobectomy tend to have poor retention in retrospective studies because patients tend to stop visiting their doctors when they are feeling well. The difference in retention between patients of near-total or total thyroidectomy and patients of lobectomy is rarely ever mentioned in retrospective studies. But this helps explain why some investigators found no significant difference in recurrence between the two procedures[32)33)].

And on top of all this was the professional bias of individual investigators. In the absence of a randomized trial, doctors generally do not perform treatments they do not believe in, due to which single-institution retrospective studies tend to have poorly structured control groups. Shiro Noguchi performed over ten thousand thyroid surgeries during his career by official record, not counting the thousands he hijacked while nominally assisting or overseeing them. He employed clerks whose sole mission was to stay in contact with his postoperative patients by telephone and mail, and to do detective work to track down their ever changing addresses. As a result, he published a number of long-term retrospective studies with large populations and excellent patient retention. His focus, however, was to prove the validity of prophylactic lymph node dissection. He called his procedure "modified radical neck dissection" even though nearly half of his cases involved only lobectomy. His belief was, if the lymph nodes of the neck were properly excised, neither total thyroidectomy nor remnant ablation were necessary in most low-to-moderate risk cases. His support of lobectomy was only secondary to his belief in prophylactic node dissection. Another prolific surgeon Orlo H. Clark, on the other hand, was a proponent of total thyroidectomy and remnant ablation who also happened to be skeptical about the value of prophylactic lymph node dissection. Naturally, Noguchi's reports expounded on the merits of prophylactic node dissection, but compared results in the absence of remnant ablation. Clark's reports stressed the merits of total thyroidectomy with remnant ablation in the absence of prophylactic node dissection. Clark's arguments against prophylactic lymph node dissection rested on the assumption that the patient would receive remnant ablation. Noguchi did not employ radioiodine therapy in any of his cases with rare exceptions, low risk or otherwise, unless there was proven metastasis on image scans such as sonography, CAT, MRI or scintigraphy because he believed ablation was unnecessary and harmed the quality of life of his patients. Clark did not perform neck dissection unless there was proven metastasis on image scans for the same reason. Both surgeons reported excellent prognosis and low incidence of complications. (The two experts once joined hands to create a "definitive text" on thyroid cancer but the book, not surprisingly, was not a commercial success[34)].) As this example illustrates, each investigator had priorities among different points of controversy that made it difficult to compare the results of one report with another.

Other than the lack of prospective trials, varied patient retention, insufficient risk stratification and professional bias, there was also a linguistic problem. The idea that there is always some dissociation between the "signifier" and the "signified" is a relatively new concept that was not widely accepted among medical professionals of the previous generation. Authors almost never gave any thought to it. Noguchi's use of the term "modified radical neck dissection" was just one example of many idiosyncrasies in the use of terminology that hampered understanding and obstructed progress. One of the more glaring examples was Mazzaferri's use of the word "recurrence". He frequently neglected to make the distinction between "recurrence" and "biochemical recurrence"[35]. In some cases, TSH stimulation produced positive thyroglobulin serum tests in the absence of tangible metastasis on image scans. Recurrence of thyroid cancer was only implied by serum data. Such cases were termed "biochemical recurrence". The assumption was that these test results represented malignant recurrences too small to be visualized. When some doctors heard or read "recurrence" they automatically assumed that there was a detectable physical mass, but Mazzaferri was such an influential and widely cited authority that there would eventually be a school of specialists who used the term "recurrence" interchangeably with "biochemical recurrence". It takes an astute reader to realize that the "recurrence rate" in one citation is not always the same thing as a "recurrence rate" in another.

And then, in 1998, human recombinant TSH was approved for thyroglobulin testing. This was truly a product of advanced molecular biology and a cutting edge drug of a new era. It allowed testing for thyroglobulin without withdrawing replacement thyroid hormones. It would eventually be approved for use in radioiodine therapy, for which it had the same advantage. Unfortunately, the enthusiasm that this drug generated also provided incentive to perform total thyroidectomy where its necessity was still in question.

Under the influence of these persistent obstacles, some researchers continued to hone their investigative strategies with ever more refined study designs. Others seemingly decided to take the kick-in-the-teeth approach. Ito et al performed an observational study of papillary microcarcinoma and found that only 15.9% increased in size beyond the margin of error (3mm or more) and only 3.4% presented novel nodal metastasis after 10 years of observation without treatment[4]. This finding was in line with the data from unsuspected microcarcinomas found in thyroids resected for other reasons[36]. If this is the malignant potential of clinically tangible tumors, the reasoning implied, what is the clinical significance of microscopic intragrandular focci or invisible biochemical recurrence? Granted that there is evidence that post-ablative serum thyroglobulin is a predictor of recurrence in low risk thyroid carcinoma[37], an increasing number of studies suggest that routine ablation does not significantly suppress recurrence in low risk cases[38][39]. Some experts argue that remnant ablation should be performed anyway in order to prevent what little differentiated cancer that may remain from turning into anaplastic carcinoma, which is universally fatal. But the incidence of anaplastic carcinoma in North America where post-surgical ablation is performed routinely is substantially higher than the incidence in Japan where post-surgical ablation is still uncommon, although this difference has been attributed to the higher iodine content of the Japanese diet[40].

Authors on both sides of the debate have pointed out that not all papillary carcinomas are equally indolent. Some grow rapidly and progress more aggressively than others without obvious histological differences. Histological variations such as tall cell variants and

columnar cell variants have been identified[41)42)], but many unusually malignant strains cannot be morphologically identified as any different from other examples of papillary carcinoma. How to identify the rare differentiated cancers that are most likely to take a more malignant course is an important and unanswered question. Clinical risk factors are currently the only guide, although some studies on molecular prognostic markers are being performed[43)44)].

Proponents of lobectomy point out that only one recurrent laryngeal nerve is at risk when only one lobe of the thyroid is being resected thus the theoretical risk of nerve palsy is halved[45)]. Proponents of total thyroidectomy insist that the increase in complications is minimal at the hands of an experienced surgeon[46)]. Disagreement over the merits of prophylactic central node dissection is argued along similar lines[47)48)49)]. Experience suggests that the incidence of surgical complications is much more dependent on the proficiency of the surgeon than the type of surgery performed. Experts who are experienced enough to publish large retrospective studies invariably report excellent results regardless of the type of surgery they promote.

5. Where we are

So which is the better option? Is it more practical to allow a small number of recurrences and re-operate on those that recur, or ablate at the first sign of a biochemical recurrence and risk salivary gland damage to prevent re-operation? Is it more economical to periodically check for thyroglobulin with recombinant TSH, or just follow with sonogram and surgically remove the metastasis when they appear? The cost of surgery, radioiodine therapy, image scans and cytology tests vary tremendously in the US, Europe and Japan, to say nothing of the availability of high end care, the social costs of hospitalization, the geographic distance to specialized institutions and the medical legal demands on the doctor. Depending on the location of the patient and the local cost structure of medical care, one option may be more advantageous than another. At the bottom line, the current argument on low risk thyroid cancer is whether or not it is an acceptable tradeoff to allow a minimally increased risk of surgical complications to guard against a minimally increased risk of cancer recurrence when there is no proven difference in prognosis. It is difficult to reach a conclusion because the difference in benefits and demerits are so small, the choice is largely dependent on the preference and socio-economic situation of the patient. Perhaps it is time for this debate to leave the ivory tower and be presented to the patients who are directly affected.

The experts now nearing retirement or who have retired in the past few decades have lived through a vibrant age. Long ago, in an American hospital, two reputable surgeons with conflicting surgical philosophy had an argument in the operating room when, after the initial incision, they found the extent of disease to be not what they expected. Anesthesia was not as stable then as it is today and time was precious. In exasperation, one surgeon punched the other in the face, calmly changed his gloves, and completed the surgery alone while the other lay unconscious on the operating room floor. Such buccaneering days have long since ended. The controversies surrounding thyroid cancer today do not have the consequences of Crile's time when he started his crusade against radical thyroidectomy and radical mastectomy. This is an inevitable result of medical progress. As the prognosis improves and complications diminish, the persisting debates become increasingly pedantic.

Today there are surgical conferences around the world that no longer hold independent sessions for the discussion of thyroid cancer surgery. As sobering as it may sound, fading from attention is the final reward of great medical progress. We cannot be disappointed that the scope of our arguments has become smaller. Our patients are better for it.

If the past is any guide, the future of thyroid cancer treatment will most likely evolve in two major directions. One is the treatment of poorly differentiated and unresponsive cancers. The other is the ever earlier diagnosis and increasingly conservative treatment of low malignancy cancers. Endoscopic and robotic surgery that are seeing wider application in the gastroenterological field are being tested in thyroid surgery. Laser ablation and radio frequency ablation, both of which use specialized needles inserted percutaneously to ablate benign thyroid nodules, are also being tested on a limited sub-group of malignant tumors[50)51)]. If more evidence is accumulated that low-risk papillary cancers are as indolent as some researchers claim, such low invasion techniques may see wider application. The current debate on the choice between total thyroidectomy and lobectomy may seem quaint when, in the future, microcarcinomas are treated with needles tipped with thermal coagulation devises.

Conservative surgery became possible in other fields of oncology partly due to the development of adjuvant chemotherapy. Though conventional chemotherapy is not effective for differentiated thyroid cancer, tyrosine kinase inhibitors hold some promise. This new class of drugs is being tested, with encouraging results, on radioiodine refractory cases[52)], medullary carcinoma[53)] and anaplastic carcinoma[54)]. Combination therapy in the future may produce even better results.

Molecular biology has enhanced our understanding of thyroid cancer greatly. Genetic testing has allowed for early detection of MEN type 2 and prophylactic thyroidectomy[55)]. Tyrosine kinase inhibitors, histone deacetylase inhibitors[56)] and nijmegen breakage syndromes[57)] are being studied as potential new therapies for anaplastic carcinoma. Studies of micro-RNAs have provided some interesting hints in their potential for diagnosis and treatment of cancer[58)]. Further studies may present more focused differentiation of low-risk and high-risk cancers on the molecular level.

6. Summary

In summary, much has been elucidated about thyroid cancer in the past century and a half. We owe our current expertise to those who dared to challenge the status quo. The general direction of the evolution of thyroid cancer treatment has been toward lesser invasion and increasingly tailored therapy as we learned to more correctly differentiate low-risk from high-risk and acquired knowledge and confidence to leave well enough alone. The future will most likely follow this trend, differentiating the risk categories with ever greater accuracy and treating them with increasingly focused therapy. Trends to the contrary are likely to be momentary aberrations or corrections to the course. As prognosis improves and complications diminish, points of controversy in treatment options will be of increasingly smaller universal significance and will inevitably invite greater patient involvement in clinical decision making. There are still frontiers to be conquered in the field of thyroid cancer, though not as wild or lawless as in the past. There will always be room for innovators in the future. One only needs to proceed in the right direction.

(The author is a fourth generation thyroidologist. The Noguchi Thyroid Clinic and Hospital Foundation celebrates its 90th anniversary in 2012.)

7. References

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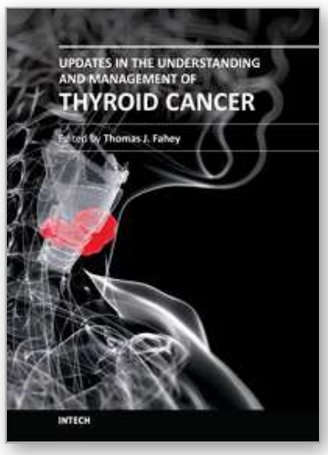

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