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Gene screening for thyroid cancer

KEYWORDS: Thyroid Neoplasms; Oncogene Proteins; Proto-Oncogene Protein c-ret; Multiple Endocrine Neoplasia; Sequence Analysis, DNA; Point Mutation; Recombination, Genetic

INTRODUCTION

The structure and function of numerous genes involved in process of carcinogenesis have been established through explosive development of molecular oncogenetics during last 15 years. Depending on the function in the cell, these genes are divided into proto-oncogenes and tumor suppressor genes. Proto-oncogenes are normal cellular genes that perform and control essential functions in the cell: growth, proliferation and differentiation. Tumor suppressor genes are normal cellular genes which carry out the control of the cellular cycle and apoptosis. Protein products of proto-oncogenes and tumor suppressor genes are found in all cellular structures / compartments. Changes in nucleotide sequence and consequently alteration of their function may generate diverse class of genes (oncogenes) that lead to the neoplastic transformation of the cell. Mutations in tumor suppressor genes lead to the complete loss of their function, which also causes the process of oncogenesis.

Several translocations involving different proto-oncogenes have been reported to be associated with a chi-like signal sequence similar to the signal sequence for the prokaryotic activator of recombination (14-16). The activity of chi-sites is reported to be influenced by their locations and by the number of chi-octamers at each site. A single chi-site stimulates recombination, but combinations of chi-sites on the two homologous are synergistic (17). In a case of chronic myelogenous leukemia (CML) in blastic crisis with t(3;21) near the breakpoint on chromosome 21, four chi-like sequences, potential consensus signals for activating recombination were found (18). In some NF1 patients, (MIM# 162200) recombination events occurred in a discrete 2-kb recombination hotspot. Recombination events were accompanied by apparent gene conversion involving the locus associated with NF1 tumor suppressor. A search for recombination-prone motifs revealed a chi-like sequence (19). Two closely spaced chi-like sequences were identified within 70-bp of the chromosome 1 breakpoint site associated with deregulation by chromosomal translocation in malignant lymphoma (20).

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At the beginning of the third millennium, the stage was set for the practical implementation of the results of molecular oncogenetics in diagnostics, prognosis, therapy, and the main objective in oncology, in preventive medicine. The implementation of standard gene tests in clinical practice of hereditary forms of cancer syndromes should primarily be emphasized (2). The basic prerequisite for the establishment of the standard gene test is that there is complete information about the structure of the carrier gene (structure of promoters, exons, introns). The second prerequisite is that there is a sufficient amount epidemiologic data that reliably correlate disease presentation with the appearance of certain mutations – adequate genotype / phenotype correlation. So far, 5 standard gene tests have been integrated into routine clinical practice – detection of hereditary mutations in the RET, VHL, AP, MEN 1 and RB genes.

The RET gene (Rearranged during Transfection) belongs to the group of proto-oncogenes and its protein product has been proven in the membrane of almost all cell types. Nevertheless, the highest level of expression of the RET protein has been confirmed in cells which originate from bronchial arches (parathyroid), the neural crest (CNS, C-cells, and thyroid), and in tissue of the urogenital system (3,4). Heredity mutations in the RET gene have been detected in persons with type 2 multiple endocrine neoplasia (MEN 2). The main characteristic of this disease is hereditary medullar thyroid carcinoma (MTC) and pheochromocytoma, each in 50% of cases, presented as 2A and 2B forms (Table 1). So far, mutation in the RET gene has been detected in 98% examined patients with a developed MEN 2A and 2B disease (4). Familial medullar thyroid carcinoma (FMTC) develops due to the hereditary mutation in the RET gene in 85% of examined families (3,4). It is interesting that the RET gene consists of 20 exons, and, in all examined cases so far, mutations have been found in only 6 exons (10, 11 and 13-16). Namely, hereditary mutations in persons with MEN 2 disease are found in two main functional domains of the RET protein: extracellular domain which binds the ligand (in persons with the MEN 2A and FMTC form) and intracellular catalytic domain (in persons with the MEN 2B and FMTC form). In over 85% of cases in persons with the MEN 2A and FMTC form, mutations appear in exon 10 in one of the 4 cysteine domains (codons 609, 611, 618, 620) and in the exon 11 (codon 634). The most frequent mutation appears in codon 634 in 80% of cases of MEN 2A and in 30% cases of FMTC (2-4). In MEN 2B, almost all cases have mutations in exon 16 and in codon 918 (4-6).

If the clinical picture suggests the possibility of hereditary nature of an established tumor one should not delay confirmation by gene tests of the MEN2 disease. A standard gene test consists of 2 main steps: the detection of the mutation and its characterization. When the screening for a hereditary mutation is involved, DNA is isolated from mononuclear blood cells, the exons of interest are amplified using the PCR technique and the detection of mutations follows. The detection of mutation is performed using different techniques of molecular genetics, and in gene tests, the so-called rapid screening techniques are used as they shorten the time necessary for analysis and they cut down the financial costs. In the analysis of RET, the technique of single strand fragments or Single Strand Conformation Polymorphism (SSCP) technique is most frequently used and direct sequencing as well. The SSCP technique, as its very name indicates, is based on the difference in conformation and consequently also on the mobility in the electrophoretic field, of single-strand DNA molecules, which can occur even as a consequence of one single basic substitution (7). The sensitivity of this technique depends on the amplicon being analyzed, and amounts to 80% to >90%, actually, there is a rare possibility for the production of false negative results, and false positive results are impossible. Contrary to the SSCP, the technique of direct gene sequencing enables absolute precision in the detection of the present mutations, so called "gold standard".

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Table 1. Tissues involved in MEN2 and mutation frequency in RET gene

Syndrome	MTC	Phaeochro-mocytoma	Parathyroid hyperplasia/ adenoma	Enteric ganglia	RET gene mutation frequency
MEN 2A	+	+(50%)	+(25%)	Normal	> 98%
MEN 2B	+	+(50%)	-	Icreased	> 98%
FMTC	+	-	-	Normal	85%

One should point out the multiple advantages of the use of gene tests in the diagnostics of a disease which is based on changes in the RET gene. The material costs of performing these tests depend on the position and general frequency of the mutation, and they are within the usual limits for the PCR method followed by nucleotide sequencing, which is incomparably less costly than the treatment of patients with a fully expressed MEN2 disease. On the other hand, a negative result of the test relieves relatives of many years of anxiety, frequent diagnostic and control examinations, the psychological burden of a possible tumor occurrence let alone family planning. Certainly, it must not be forgotten that MEN2 disease is an autosomal dominant hereditary disease, and that the person that carries a mutated allele has 50% chances for a healthy offspring, in fact offspring that will not inherit the mutated allele, which is established through the application of gene tests in prenatal diagnostics (5, 6, 8, and 9). Unfortunately, it can occur, with a probability of 50%, that the child inherits the mutated allele – a positive gene test for RET. At this point, however, it should be pointed out that a positive genetic test for RET, even in the presymptomatic stage, indicates the need for total thyroidectomy already at the age of 6 years (according to some sources, even at the age of 3 years http://www.mdanderson.org/diseases/men/display.cfm?id=c26bc4be-da65-458c-8943e0dd3d1cce05&method=displayfull).

CASES REPORT

In this study we have presented just some of the results obtained through many years of practice in gene testing of mutations in the RET gene.
Figure 1. shows part of the nucleotide sequence (graphic recording ABI 377 of the nucleotide sequencer, in which every peak determines one nucleotide in the DNA chain) in exon 10 of the RET gene of a patient with medullar carcinoma of the thyroid gland. The figure clearly shows two overlapping peaks in the position of codon 618, which indicates two different alleles: the wild type and a mutated allele.

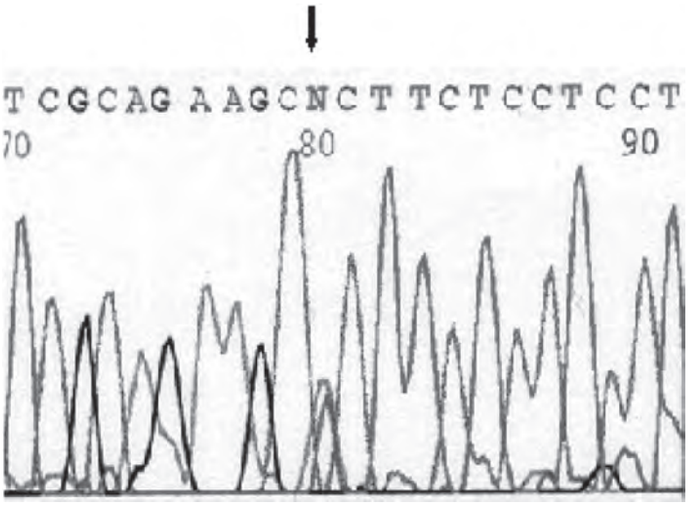

Figure 1. Determination of type and position of mutation by gene sequencing. Arrow shows two overlapping peaks (heterozygote) i.e. position of mutation in codon 618, exon 10 of RET gene: wild codon type (TGC) and mutated codon AGC

Also, mutations in introns of the RET gene have been only rarely described in hereditary cancer syndromes of the thyroid and diseases related to abnormalities in the neural crest development. It was reported that a patient had lost exon 10 in the tumor mRNA as a result of the deletion of the dinucleotide AG at the 3'-splice acceptor site of intron 9. This molecular defect was only found in the tumor DNA. A point mutation at the splice acceptor site of intron 12 was detected in patients with aganglionosis of the total colon. These findings have been amply reviewed (10-15).

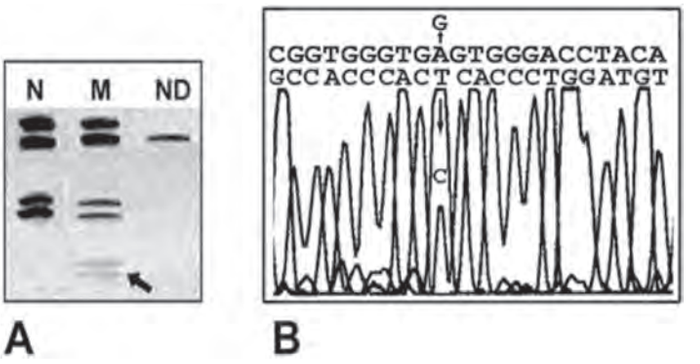

Figure 2. Sequence analysis of the RET proto-oncogene. Panel A shows SSCP profiles of the amplicon of the exon 10 including the flanking region of the intron 10. The arrow indicates variant electrophoretic bands. N, M, and ND stand for DNA from tissue of healthy volunteers (N), patient's tumor tissue (M), and non-denaturated DNA (ND), respectively. In panel B the sequencing profile demonstrates segment of the amplicon with overlapping T and C peaks

Gene testing for presymptomatic identification of individuals at risk in affected families provides the most reliable indication for prophylactic thyroidectomy if the constitutional mutation is detected. There is consensus for the need for more novel mutations that are expected to generate a better understanding of the risk for each mutation associated with disease. In this context, our result is an addition to the needed database with phenotype – genotype correlations and is expected to aid the front line therapy in the treatment of multiple endocrine neoplasia.
A female patient, age 55, was hospitalized and subjected to surgery due to polynodular thyroid gland at Institute for Radiology and Oncology of Serbia in Belgrade. We had to perform total thyroidectomy due to carcinoma found in the upper left lobe, 8 x 5 x 7 mm in diameter. The final histopathology findings revealed Carcinoma microfolliculare gl thyroideae with differentiation towards medullar type. RET gene analysis was conducted according to the Consensus Guidelines (4). DNA was isolated from excised tissue and peripheral blood as previously described (21). Control DNA was obtained from blood samples donated by five presumably healthy laboratory volunteers. Amplification RET exons 10, 11, 13, 14, 15 and 16 was accomplished with primers that allow for inclusion of parts of intronic sequences into respective amplicons (23). Routine mutational screening was performed by single stranded conformational polymorphism (SSCP) (7). Variant electrophoretic bands resolved on the silver stained gels were indicative of sequence alteration. In a separate experiment, the PCR amplicon that generated variant electrophoretic bands upon SSCP analysis, was resolved on a gel and gently removed with a hypodermic 22-gauge needle pre-wetted with the PCR master mix solution. The needle was dipped in the PCR reaction mix for 2 minutes and then discarded. This PCR product was reamplified with the same primers used to generate this amplicon using the same PCR profile. This DNA was subjected to direct cycle sequencing in both directions using fluorescent dideoxy terminators on the automated sequencer Prism 310 from Applied Biosystems, Foster City, CA.
DNA isolated from peripheral blood of laboratory volunteers was compared with DNA isolated from both tumor tissue and peripheral blood of the patient. The optimized SSCP screening clearly demonstrated variant electrophoretic bands indicated by the arrow (Figure 2, panel A). The same result was obtained with the tumor tissue DNA and constitutive DNA documenting

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germline nature of the sequence alteration. Reamplified and sequenced DNA demonstrate the presence of two alleles, one with the sequence of the normal consensus RET proto-oncogene and one with an altered DNA sequence. The sequence alteration, visualized as overlapping peaks in the sequencing profile, demonstrate heterozygosity and the A to G base substitution (Figure 2, panel B).

The substitution occurs at the beginning of the intron 10 in the RET proto-oncogene denoted as IVS10+4G. This is shown in the part of the sequence of the analyzed amplicon (Figure 3).

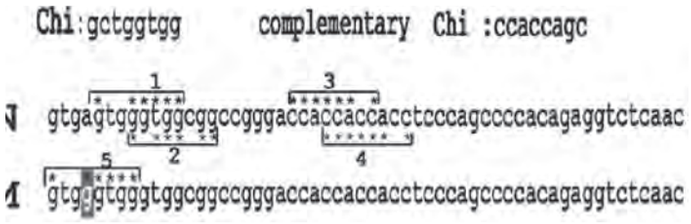

Figure 3. The sequences of the beginning of the RET intron. Panel N shows four chi-like sequences in the wild – type sequence labeled 1 through 4, respectively. Sequences 3 and 4 are complementary to the chi-like consensus. Symbols * stand for perfect homology with the chi consensus sequence. Panel M shows alteration resulting in G (shaded) in the analyzed amplicon and consequently newly generated chi-like sequence labeled 5

Closer inspection of the intron 10 (Figure 3) reveals several important features. In the immediate neighborhood of the substitution, there are four chi-like sequences. They are labeled 1 through 4. The first two are on the coding strand with the sequence homology of 6 out of 8 bases of the consensus GCTGGTGG. On the non-coding strand, sequences labeled 3 and 4 have sequence homology 7 out of 8 of the consensus. Both of the pairs of sequences are overlapping and only several nucleotides apart. In described patient, the A to G base substitution generates the 5th chi-like sequence overlapping the first two.**

Molecular oncogenetics has entered the third millennium with standard gene tests, creating, primarily, conditions for efficient prevention. Namely, the mutations that are the cause of the disease can be detected in the presymptomatic phase and in the prenatal stage, with the objective of securing prevention and avoiding many times more costly treatment, more costly not only in the financial sense. In order to determine a hereditary mutation that poses a 100% risk of the development of a tumor, only 5 ml blood is necessary, and, what is of crucial importance in both the financial and the psychological sense, an analysis is carried out only once in a lifetime.

DISCUSSION

Multiple endocrine neoplasia type 2 (MEN 2) is an inherited disease caused by germline mutations in the RET proto-oncogene and is responsible for the development of endocrine neoplasia. Its prognosis is depend ent on the appearance and spread of medullary thyroid carcinoma (MTC). Relatives at risk can be identified before clinical or biochemical signs of the disease become evident. Genotype – phenotype correlations in this pathology remain in the focus of medical and scientific research (24,25). The sequence-specific differences in the clinical presentation of this cancer and the familial rates suggest that the risk of progression was based on the transforming potential of the individual RET mutations. For this reason, expanding the database of sequence alterations in the RET proto-oncogene related to specific disease phenotypes continues to keep this research high ranking in the area of gene testing in medicine.

In this report, we described atypical MTC case in patient where the carcinoma presented not as fully developed medullar carcinoma but as microfollicular carcinoma with tendency to evolve into MTC. Molecular characterization of the constitutive and tumor tissue DNA revealed novel germ line sequence alteration in the intron 10 of the RET proto-oncogene. The atypical clinical presentation correlates with unusual type of the base substitution. Namely, the substitution generates a novel chi-like sequence overlapping two existing chi-like sequences on the same DNA strand and is in close vicinity of the two existing chi-like sequences on the opposite strand. An octamer (GC[A/T]GG[A/T]GG) similar to the chi (GCTGGTGG) bacterial recombination element has been reported at sites close to somatic recombinations in tumors (18). As outlined in the Introduction of this report, sequences with homology with the chi have been associated with several types of DNA alterations linked with human cancer. In the view of the concept that this type of sequences may act synergistically to promote recombination, described generation of the new among existing multiple chi-like sequences may point to a new type of oncogenic potential of altered RET oncogene. This is in accordance with the widely accepted model of multi-step of carcinogenesis where described sequence alteration may enhance genome instability. This instability is likely to provide the cancer with an advantage in terms of faster progression through the many stages of tumorigenesis (19) and described data may represent yet another mechanism of this accelerated progression.

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Surgery of thyroid carcinoma

KEYWORDS: Thyroid Neoplasms; Surgery; Medical Oncology

Surgery is the initial therapy in thyroid carcinoma. The basic principles of surgical oncology in malignant epithelial tumors is fully considered in thyroid carcinoma (TC). The surgery is performed on organ of tumor origin and regional lymphatic basins. The aim of surgery in thyroid carcinoma is to eradicate all tumor foci, cure the most number of patients, reduce recurrence and mortality rate, and provide good quality of life.
Undoubtedly, the surgery for thyroid carcinoma has no alternative. The extent of surgery is matter of actual controversies (1-15).
Postoperative radio-iodine ablation is proposed for patients with high risk for recurrence. External radiotherapy is indicated in older patients (over 45 years at diagnosis) with residual tumor without radio-iodine up-take.
The extent of primary surgery should be dictated by stage of disease and prognostic factors. The quality of surgery and incidence of complications depends on surgeon's skill and experience. That is why the surgeon is factor of prognosis in treatment of patients with TC (16).

Pre-operative diagnosis and evaluation

Clinical examination is the key stone in diagnosis of TC. Ultrasound of the neck is the next step and it is very informative. Fine needle aspiration biopsy of thyroid nodule or neck lymph node for cytology examination is inevitable part of pre-operative diagnostic.
Indirect laryngoscopy and ORL examination gives the information of vocal cord status in cases of laryngeal nerve infiltration with local tumor growth.
Chest X-ray, bone scan, ultrasound of abdominal organs, blood tests, hormonal thyroid status, serum thyreoglobulin and calcitonin levels, as well as scintigraphy, computed tomography (CT) or magnetic resonance imaging (MRI) of mediastinum if indicated enables detection of initial distant metastases.
Before the operation the patient should be informed about surgical procedure and eventual complications (laryngeal recurrent nerve injury, hypocalcaemia) and examined by anesthesiologist.

Surgery of thyroid gland

Surgery for TC, as in all malignant epithelial tumors, includes surgery of organ of tumor origin and surgery of regional lymph nodes i.e. thyroid gland and neck lymph nodes as well as mediastinal lymph nodes if indicated.

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The extent of operation is planned according to tumor stage and other prognostic factors including experienced thyroid surgeon. Tumor stage is obtained by frozen-section histopathology examination of thyroid gland, neck lymph nodes, surrounding soft tissue and eventually parathyroid glands in cases of infiltration.
The complete operation should be performed in the same act in order to avoid re-operation and to reduce percent of complications i.e. laryngeal nerves and parathyroid glands injury (16).
The extent of primary operation is debated. The best results are achieved with total or "near" total thyroidectomy and appropriate dissections of neck and mediastinal lymph nodes.

Choice of operation

Nodectomy or partial lobectomy is not suggested because of high percent of recurrences (3,7,12).
Total lobectomy is the minimal surgical procedure for thyroid nodule. It is followed with minimal complications, but unfortunately laryngeal nerve injuries are registered.
"Near" total thyroidectomy includes removal of affected lobe, isthmus and almost the entire opposite lobe except small amount of thyroid tissue (1 gr) in Berry's ligament.
With total thyroidectomy the whole thyroid gland, including pyramid lobe, is removed.
The surgery of thyroid gland is the surgery of laryngeal recurrent nerve and parathyroid glands. The parathyroid glands should be preserved on venous-arterial stalks (17,18). If the gland is operatively removed it could be implanted in sternocleidomastoid muscle (acc Wells) (19). Intra-operative mapping of parathyroid glands with metilen blue stain is helpful in some cases (20).

Advantages of total and "near" total thyroidectomy

- The complications are extremely rare when they are performed by experienced surgeon (16).
- Post-operative TSH suppression is indicated in all patients with differentiated thyroid carcinoma (DTC), so less radical operations are not justified (13).
- Histological studies of the opposite lobe have shown the high incidence (30%-82%) of bilateral multufocality in papillary thyroid carcinoma (PTC) (3). After lobectomy, local recurrence rate is 5%-24%. De Groot have shown significantly higher survival rate after "near" total thyroidectomy versus lobectomy or subtotal thyroidectomy in patients with papillary thyroid carcinoma greater than 1 cm in diameter (21).
- Total or "near" total thyroidectomy facilitate follow-up and detection of distant metastases in differentiated thyroid carcinoma. After total thyroidectomy serum thyroglibulin levels are excellent marker of disease recurrence. In cases of thyroid remnant, I-131 scan is not the most efficient in early detection of local or distant recurrence. Also, ablative radio-iodine treatment is more efficient after radical surgery.

Mazzaferri reported a significant reduction (up to 50%) of recurrence after total or "near" total thyroidectomy in stage 3 and 4 tumors in PTC, comparing to less radical surgery (22). The incidence of recurrence in the first two years after initial surgery is four times higher in patients with PTC treated with lobectomy compared to "near" total or total thyroidectomy (26% vs. 6%) (23). The same group has found that cancer specific mortality is two times higher with less radical surgery (24). Also, overall survival is significantly improved with "near" total or total thyroidectomy in high risk PTC and non-Hurthle-cell FTC (25).
According to novel studies, the extent of surgery in FTC is not as important as in PTC. However, total thyroidectomy in FTC enables more confident follow-up and facilitate diagnosis and treatment of distant metastases.
In cases of solitary papillary micro carcinoma lobectomy could provide excellent long-term outcome. Nevertheless, in cases of multifocal micro carcinoma, total thyroidectomy is the surgery of choice (26).

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In conclusion, the advantages of total and "near" total thyroidectomy are: lower recurrence rate, better survival, increased sensitivity of thyroglobulin as tumor marker, decreased indications for radio-iodine ablation, low complications rate when performed by experienced surgeon. L-Thyroxin suppression is indicated in all patients with DTC even if less radical surgery is performed.

Surgery of lymph nodes

Choice of operation

Thyroid carcinoma metastasize in central (pre- and para-tracheal) and lateral (jugulo-carotid, supraclavicular) neck lymph nodes. The incidence of lymph node metastases in PTC is 30%-80%, up to 95% in children, while in FTC is very low (20%) (2).

Lymph node metastases (LNM) are most common on the side of primary tumor. Also, metastatic spreading depends on tumor localization. Most often, lymph node metastases were found in pre-, para-tracheal (central) region of the neck and upper anterior mediastinum, and jugulo-carotid (lateral) region. The incidence of LNM depends on histology type, tumor stage and extent of dissection, as well as precise pathohistology examination of obtained specimens.

Staging and therapeutic dissections are suggested instead of visual staging. Dissection of central and biopsy of supraclavicular and lower third of jugular chain of neck lymph nodes is the integral part of thyroid cancer surgery, together with total thyroidectomy. This operation is called total extended thyroidectomy. Only surgically removed and histology examined lymph nodes, if they are not metastatic, could be staged as pN0.

Lymph node metastases are associated with high risk of loco-regional recurrence and distant metastases. Gross lymph node metastases in the neck, as well as bilateral and mediastinal metastases significantly decrease survival rate in patients with DTC (22,28,29).

Lymph node metastases in lower third of jugulo-carotid chain have high predictive value (80%) of LNM in upper two thirds. In that case modified radical neck dissection (MRND) is indicated in the same act. Preservation of internal jugular vein, sternocleidomastoid muscle and accessory nerve is mandatory. Dissection is performed through oblique skin incision or through prolonged horizontal incision for thyroidectomy. Dissection of upper anterior mediastinum till aortal arc is performed through the same incision (30,31).

Sternotomy is indicated in massive mediastinal lymph nodes and it is performed under the tracheal bifurcation.

In FTC, dissection is performed in the same manner in cases of lymph node metastases on frozen-section examination (26,29).

Advantages of central neck dissection

- It enables precise staging of the disease, as in all epithelial malignancies. Intraoperative detection of LNM also enables immediate therapeutic dissections in the same act.
- It facilitates postoperative follow-up and improves ablation with I-131.
- It is the therapy of choice in thyroid cancer that doesn't uptake I-131.
- Re-operation in paratracheal region carries a high risk of laryngeal nerve and parathyroid glands injury (9).

Sentinel lymph node biopsy

Concept of sentinel lymph node biopsy (SLNb) was widely studied in last decade. In differentiated thyroid carcinoma it was first introduced by Kelemen (32), and followed by few similar studies. Altogether, the the identification rate was 66% to 100%, with sensitivity for lymph nodes from 80% to 100% using blue dye and/or lymphoscintigraphy (Tc99m) methods (33).

A prospective study of SLNb using metilen blue dye, performed in the Institute for Oncology and Radiology of Serbia, comprised 40 patients with DTC. The study was aimed to establish the accuracy of the SLNb method to support intraoperative decision to perfom modified radical neck dissection in respect to frozen section examination of SLN in lower jugulo-carotid chain. Overall identification rate was 92.5%, with accuracy of 95% (34).

Re-operations

Despite good prognosis of differentiated thyroid carcinoma, locoregional relapse occurs in 5% to 20% of patients, most often in the first 5 years after inital surgery. Relapse usually occurs in thyroid bed after incomplete operation of thyroid gland or in cases of locally agressive variants of carcinoma, and/or in not dissected lymph nodes of the neck.

If not visible on ultrasound or CT scan, the whole body scintigraphy (WBS) with I-131 could visualize tissue remnant using intraoperative gamma probe and excised (35).

Indications:

- In cases of cancer or LNM found on definitive histology after false negative result on frozen-section
- In cases of incomplete primary operation with rest tumor or thyroid tissue, or presence of LNM in the neck or mediastinum.

Surgical complications

Transient or permanent hypoparathyroidism and laryngeal nerve paralysis are the most common and the most serious complications in thyroid cancer surgery. The incidence of complications depends on surgeons skills. The incidence of laryngeal nerve paralysis is below 5% and permanent hypoparathyroidism is below 2% (22).

Surgery for medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) is multifocal in 90% of hereditary carcinoma, and in 32% of sporadic forms. When the tumor is palpable, lymph node metastases are present in more than 50% of cases (25%-63%), and about 20% of patients have distant metastases.

Operation comprise total thyroidectomy, dissection of central neck compartment including upper mediastinum, as well as functional lateral neck dissections from facial vein to supraclavicular region. If there are gross lymph metastases, modifed radical neck dissection should be performed. Total thyroidectomy is indicated in both sporadic and hereditary MTC, because C-cells have diffuse and bilateral distribution in thyroid tissue. However, surgery for MTC also includes visualization (metilen blue staining) and exploration of all four parathyroid glands. In cases of adenoma or hyperplasia the affected glands should be removed and histology examined. All MTC patients should be pre-operatively screened for MEN syndrome (pheochromocytoma, etc). Genetic screenig for hereditary forms is also advocated (36,37).

Surgery for anaplastic thyroid carcinoma

Anaplastic thyroid carcinoma is always fatal. Due to extremely fast growth of tumor mass with infiltration of trachea and surrounding structures, patients usually die of choke within 3 to 6 months. The role of surgery, if it is possible, is to provide the reduction of tumor and deliberate trachea as much as possible, and to relieve breathing and/or provide placement of permanent tracheal canila.

Surgeon as a prognostic factor

It is necessary to emphasize that thyroid cancer surgery should perform only a surgeon well trained in that field of surgery. The first evidence was Theodore Kocher who declined the thyroid surgery complication mortality rate from 40% to 1%, after 5000 operation performed (16).

The novel studies have shown that incidence of postoperative complications could be lesser than 0.5% when performed by experienced surgeons. Furthermore, some studies have found that completeness and quality of primary operation improves the long-term disease free survival and quality of life (16,38).

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Radiotherapy of thyroid cancer

KEYWORDS: Thyroid Neoplasms; Radiotherapy; Brachytherapy; Carcinoma, Papillary, Follicular; Carcinoma, Medullary; Lymphoma

Surgery is primary treatment modality of thyroid gland malignant tumors. Success of radiotherapy depends on extent of previously performed surgical treatment. Radiotherapy can be curative (profilactic and postoperative) and palliative by its intent. Tumor dose and irradiation technique depend on tumor histology type and extent of previously performed surgical treatment as well as palliative and curative aim and patient's objective condition (1).

External beam radiotherapy for differentiated thyroid cancer

Surgical resection, usually combined with radioiodine, is the mainstay of treatment of differentiated thyroid cancer. External beam radiation therapy has a secondary role with respect to metabolic RT and is used for the scarcely captating tumors and those that are resistant to radioactive iodine treatment at the usual doses (2).

The optimal management of locally advanced differentiated thyroid cancer is controversial. Retrospective outcome studies remain the most reliable way of assessing therapeutic efficacy but are hampered by significant heterogenity in diagnostic evaluation, staging, and treatment strategies that have evolved over time (3-5).

Early reports suggested that EBRT was either ineffective or even associated with a worse outcome (6). The latter may have been because of selection bias or suboptimal treatment techniques. More recent series have consistently shown a favorable impact on local-regional control. Tubiana et al. (7) reported on 163 patients with either microscopic or gross residual disease following surgery; the 15-year local-regional control rate was 89% after EBRT compared with 67% after surgery and radioactive iodine. Ninety-seven patients had an 85% local-regional control rate after EBRT following macroscopically incomplete surgery for 17 patients with inoperable disease, the 5-year relapse-free survival and overall survival rates were 55% and 60%, respectively. Tsang and coworkers (3) reported 155 patients with papillary thyroid carcinoma who had microscopic residual tumor after surgery. Patients who received EBRT had a 93% 10-year local-regional control rate compared with 78% for those who were not irradiated. Those who received EBRT also had a significantly improved cause-specific survival rate (3). In a series of 163 patients with stage pT4 lesions treated with total thyroidectomy, remnant ablation, and suppressive thyroid hormone therapy, Farahati et al demonstrated marked improvement in both local-regional control and disease-free survival for those older than 40 years who were treated with doses of 50 to 60 Gy (8). Simpson et al noted marked improvement in local-regional control and overall survival in patients with differentiated thyroid cancer who had microscopic residual disease after surgery and received EBRT (9).

There is paucity of dose-response data for differentiated thyroid cancer (3,7,11). Tubiana et al observed a 5% in-field recurrences rate for patients treated to an average dose of 50 Gy with megavoltage EBRT compared with 15% and 22% for patients treated to lower doses with orthovoltage EBRT and radium molds, respectively (3). There were no local-regional recurrences in patients treated at Department of Radiation Oncology, University of Florida, to doses in excess of 64 Gy, suggesting that there may be a dose-response relationship (10).

Based on review of the literature, recommendations for EBRT are as follows:

1) after a total thyroidectomy with lymph-node neck dissection, EBRT is given for patients older than 45 years who have positive margins, extra thyroidal extension, and/or extra capsular nodal disease,
2) for local-regionally recurrent disease, EBRT follows surgery in patients older than 45 years
3) unresectable gross disease except for the rare pediatric case where EBRT is delayed as long as possible. In younger adult patients (younger than 45y) the decision on how to treat is clinically based on a combination of factors including adequacy of prior I-131 therapy, thyroglobulin level, and the presence of distant metastases (10).

Recommendations for tumor doses are very different: from 50 Gy in 5 week with conventional fractionation for sub clinical disease to 64 or 66 Gy for same indication (1,12).

For macroscopic disease recommendations are from 65 Gy in 7 weeks (180-200 cGy per day) to 72 Gy in 42 fractions using a concomitant boost technique, administered with intensity-modulated radiation therapy (4,8,10).

Hurthle cell carcinoma (HCC) of the thyroid gland is a rare neoplasm that comprises 2% to 10% of all differentiated thyroid cancer. Total thyroidectomy is the mainstay of treatment for HCC. The role of conventional external beam radiation therapy in the treatment of HCC has not been well-described.

Foote et al suggests that HCC of thyroid gland is a radiosensitive tumor. Patients presenting with symptomatic distant metastasis or unresectable recurrent disease in the neck and mediastinum should be referred for consideration of palliative radiation therapy. Patients with large invasive tumors, even when those tumors were apparently resected completely, may benefit from adjuvant radiation therapy, particularly when nodal metastases, vascular invasion, soft-tissue invasion, or DNA aneuploidy is present (13).

Stewart et al prescribes a radiation dose of 55 Gy in 30 fractions over 6 weeks to an extended tumor volume (neck and upper mediastinum) in patients with suspected microscopic residual tumor (14).

For palliative treatment Foote has been recommended doses of 20 to 30 Gy. Lower doses led to more frequent retreatment and a shorter duration of symptom relief (13).

External beam radiotherapy for medullary thyroid cancer

Medullary thyroid carcinoma MTC is a rare tumor derived from para follicular or C cells of the thyroid, accounting for 5%-10% of all thyroid malignancies. Prognosis of MTC is generally regarded as being intermediate in severity between anaplastic thyroid cancer and differentiated thyroid cancer although duration of survival is very variable. The biological behavior and prognosis depend on the type of tumor: the sporadic form has an intermediate prognosis, patients with multiple endocrine neoplasia type 2a (MEN 2a) have a better prognosis and with MEN 2b have a poor prognosis (15).

The initial, potentially curative treatment for MTC is surgery consisting of total thyrodectomy plus dissection of lymph nodes in the central compartment of the neck. In addition, patients with cervical lymph-node spread require modified neck dissection (16).

External beam radiation following surgery may help in the control of local disease (17).

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In the absence of prospective randomized trials, the place of external radiotherapy in the management of MTC is uncertain with varying claims made in the literature of the benefits or otherwise of this treatment. Samaan et al noted a better overall survival in those not treated with irradiation which persisted after matching for extent of disease (18). However, in a large series from Texas the lower survival in patients receiving RT could be attributed to their more advanced disease at presentation. Since RT was given to patients with more advanced disease, their similar survival rate could suggest a beneficial effect (15).
Favorable effects of RT was reported by Hyer et al in patients with residual microscopic disease after surgery and in patients with disease spread to local lymph nodes showing significantly reduced local relapse rates. Small foci of residual tumor can be eradicated with doses of 60 Gy over 6 weeks. External beam radiotherapy is indicated when surgical excision is impossible or incomplete and than should be given doses of 66 Gy over 7 weeks (19). In patients considered to be at high risk of local/regional failure, if the postoperative calcitonin level is high despite adequate neck node disssection and there is no evidence of distant metastasis then postoperative external radiation is given (20,21).
Postoperative RT should be given to patients with microscopic residual disease which cannot be removed surgically without undue morbidity. RT to radical dose is also recommended in patients with inoperable or recurrent loco-regional disease; some of these patients may subsequently be rendered operable. Metastatic disease may gain worthwhile palliation of otherwise uncontrolled neck disease, or painful bone metastases (17).

External beam radiotherapy for anaplastic thyroid cancer

The prognosis of anaplastic carcinoma is dismal and has not changed in the last 20 years. Median survival is usually between 3 and 6 months with less than 5% of patients surviving 3 years. Patients present with advanced disease, a rapidly increasing neck mass is the most common presenting symptom. Most patients have inoperable tumors invading the trachea, pharynx and great vessels. Even when patients have technically operable tumors their age and frailty makes radical treatment impossible Anaplastic tumors do not concentrate iodine and external irradiation is often only palliative. Although these doses do not prolong survival, there is usually shrinkage of the primary mass and adjacent confluent lymphadenopathy with high dose treatment. Stridor resulting from obstruction (often at a level too low for tracheostomy) can be relieved and patients unable to swallow their own saliva can have deglutition return to normal.
Pain resulting from bone metastases can be relieved with a single large-fraction external beam treatment (4).
Both physical and biological optimization of external beam radiotherapy is required to improve the poor control of locoregional disease.
Over the last 20 years, there has been an increasing interest in using aggressive radiotherapy regimens often combined with synchronous chemotherapy in an attempt to achieve local control and cure a small proportion of selected patients.
Tallroth et al. reported 15 objective responses out of 25 patients when combined hyper fractionated radiotherapy (total dose 46 Gy in 1 Gy fractions given twice daily) and concomitant chemotherapy was used. 12 patients demonstrated local control at the time of death with a median survival of 4 m. There were two long-term survivors, both of whom underwent total thyroidectomy following chemotherapy plus radiation (22).
There has also been trend in the last decade for using accelerated radiotherapy regimens for anaplastic carcinomas. The theory is that these tumors have a high proliferative rate and that accelerated radiotherapy allows the tumor cells less time to divide during treatment.
Mitchell et al reported 10 objective responses out of 17 patients when patients were treated twice daily, 5 days a week to a TD of 60, 8 Gy in 32 fractions over 20-24 days. Two patients died before radiotherapy was completed. Toxicity from oesophagitis and dysphagia was high with 10 patients requiring intravenous fluids or nasogastric tube feeding (23).
New treatments for anaplastic thyroid carcinoma are desperately needed. The radiobiologic impact of intensity modulation for this tumor should be further tested clinically (24).

External beam radiotherapy for thyroid lymphoma

The prognosis and treatment of anaplastic carcinoma and thyroid lymphoma are so different that it is imperative to do differentiation between this two entity. For stage I and II moderate – dose radiotherapy should always be delivered: 40 Gy over 4 weeks usually achieves local control even in patients with unresectable disease (25). For stages I and II disease, initial chemotherapy by using CHOP protocol was the preferred treatment at in some centers, with irradiation being given later. Combined therapy were given to all patients except those with small bulk disease under 3cm in size confined to the thyroid. Patients with stage III or IV disease require chemotherapy, with subsequent irradiation only if bulk disease persists in the neck (26).

Radiotherapy techniques

Choice of optimal radiotherapy technique in treatment of the thyroid carcinomas is not easy task for irradiation oncologist, due to topographic relation of this organ and its lymph drainage. Closeness of medulla spinalis and changeable neck thickness make this tumor especially difficult for treatment. Treatment volume in transversal neck section has horseshoe shape, including the thyroid bed, adjacent tissue at risk for tumor infiltration and regional lymphatic. Upper mediastinum can also contain tumor, either by direct invasion from thyroid bad or by lymphatic spread from brachiocephalic nodes.
Treatment volume usually extend from angle of mandibila to bifurcation of trachea.
Presentation of regions of interest by imaging procedures (computerized tomography and magnetic resonance) is basis for radiotherapy planning and choice of irradiation techniques. At referent sections we define GTV, CTV, PTV and structures of risk.
The most common radiotherapy techniques are:
- one direct field,
- two opposite parallel fields,
- two opposite oblique fields (27).

Radiotherapy is planned in two acts:

In the first act tumor dose of 40-45 Gy is given from one direct or two opposite parallel fields by x or gamma beams with homogenization of the dose by compensation filters and with modification field by lead block for the lungs parenchyma protection.

Tumor dose of 15-20 Gy is given in the second act:

- by X photons and oblique fields with use of wedge filters. In that way the region of the neck and front upper mediastinum is irradiated and spinal cord is avoided.
- by electrons beam with or without mulage from one direct field on tumor bed and jugular region if there is no spreading into mediastinum. Influence on the spinal cord is avoided with correct choice of depth (21).

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