specific proteins mentioned above could be detected in serum, they also have the potential to provide a new generation of serum markers for breast cancer.

References

1. Duffy MJ. Serum tumour markers in breast cancer: are they of clinical value. Clin Chem 2006; 52: 345-351.
2. Cheung K, Graves CRL, Robertson JFR. Tumour marker measurements in the diagnosis and monitoring of breast cancer. Cancer Treat Rev. 2000; 26: 91-102.
3. Anonymous. Clinical practice guidelines for the use of tumour markers in breast and colorectal cancer. J Clin Oncol 1996; 14: 2843-2877.
4. Duffy MJ, Duggan C, Keane R, et al. High preoperative CA 15-3 concentrations predict adverse outcome in node-negative and node-positive breast cancer: study of 600 patients with histologically confirmed breast cancer. Clin Chem 2004; 50: 559-563.
5. Bast RC, Ravdin P, Hayes DF, et al. 2000 Update of recommendations for the use of tumour markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19: 1865-1878.
6. Blamey RW. Guidelines on endocrine therapy of breast cancer, EUSOMA. Eur J Cancer 2002;38:615-634.
7. Pestalozzi BC, Luporsi-Gely E, Jost LM, et al ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer. 2005; 16 (Suppl 1): 7-9
8. Molina R, Barak V, van Dalen A, Duffy MJ, et al. Tumour markers in breast cancer: European Group of Tumour Markers (EGTM) recommendations. Tumour Biol 2005; 26: 281-293.
9. Fleisher M, Dnistrian AM, Sturgeon CM, et al. Practice guidelines and recommendations for use of tumour markers in the clinic. In: Diamindis EP, Fritsche H, Scharwtz MK, Chan DW, eds, Tumour markers, physiology, pathobiology, technology and clinical applications, Chicago: AACC Press 2002: 33-63.
10. Robertson JFR, Jaeger W, Syzmendera JJ, et al. The objective measurement of remission and progression in metastatic breast cancer by use of serum tumour markers. Eur J Cancer 1999; 35: 47-53.
11. van Dalen A, Heering KJ, Barak V et al. Treatment response in metastatic breast cancer: a multicenter study comparing UICC criteria and tumour marker changes. The Breast 1996; 5: 82-88.
12. Kurebayashi J, Nishimura R, Tanaka K, et al. Significance of serum tumour markers in monitoring advanced breast cancer patients treated with systemic therapy: a prospective study. Breast Cancer 2004; 11: 389-395.
13. Watson MA, Dintzis S, Darrow CM, et al. Mammaglobin expression in primary, metastatic, and occult breast cancer. Cancer Res 1999; 59: 3028-31.
14. Jiang Y, Harlocker SL, Molesh DA, et al. Discovery of differentially expressed genes in human breast cancer using subtracted cDNA libraries and cDNA microarrays. Oncogene 2002; 21: 2270-82.
15. O'Brien N, Maguire TM, O'Donovan N, et al. Mammaglobin a: a promising marker for breast cancer. Clin Chem 2002; 48: 1362-4.
16. Colpitts TL, Billing-Medel P, Friedman P, et al. Mammaglobin is found in breast tissue as a complex with BU101. Biochemistry 2001; 40: 11048-11059.
17. Houghton RL, Dillon DC, Molesh DA, et al. Transcriptional complementarity in breast cancer: application to detection of circulating tumour cells. Mol Diagn 2001; 6: 79-91.
18. Miksicek, R J, Y. Myal Y, Watson PH, et al. Identification of a novel breast- and salivary gland-specific, mucin-like gene strongly expressed in normal and tumour human mammary epithelium. Cancer Res 2002; 62: 2736-40.
19. Bertucci F, Birnbaum D, Goncalves A.Proteomics of breast cancer: principles and clinical applications. Mol Cell Proteomics 2006 Oct; 5 (10): 1772-86.
20. Colpitts TL, Billing P, Granados. E, et al. Identification and immunohistochemical characterization of a mucin-like glycoprotein expressed in early breast cancer. Tumour Biol 2002; 23: 263-278.

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Diagnosis and treatment of thyroid cancer: a view from the Dutch consensus

T.P. LINKS

Thyroid cancer is a rare cancer, with an incidence of 1/100,000 in men and 3/100,000 in women. This results in about 350 new patients every year in the Netherlands.

For the overall survival is good, the prevalence is relatively high 1/4000, resulting in about 4000 patients in the Netherlands (1). Histologically several subtypes of malignant thyroid tumours can be distinghuished: the differentiated (papillary, follicular and Hürthle) carcinoma originating from the follicular epithelium, the medullary carcinoma consisting of malignant transformed C cells, and the anaplastic carcinoma, ofter considered to represent the terminal stage in the dedifferentiation of a thyroid tumour.

Recently, it has been reported that the incidence of thyroid cancer has been increased with 2.4 fold in the United States, but the overall mortality has been remained stable. This increase is attributable to the increase of small papillary thyroid cancers, reflecting early detection or subclinical disease (2).

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Treatment of thyroid cancer

Surgery is the cornerstone of treatment, When an uni-

focal papillary carcinoma < 1 -1,5 cm (occult) is present the prognosis is that good that, only an (extended) hemi-thyroidectomy can be executed not followed by ablation therapy with 131-I. In all other thyroid cancer a (near-total) thyroidectomy must be done, with lymph node dissection if indicated.
After a total thyroidectomy an ablation therapy with I-131 must be given for several reasons: -to destroy the rest of the normal thyroid tissue, that had been left by the surgeon -to support 131-I uptake in thyroid cancer tissue, -to make it possible to use thyroglobulin as a tumour marker in the follow-up and -to treat microscopical or (if surgical removal is not possible) macroscopical cancer tissue.
Follow-up consists of thyroglobulin measurement during TSH suppression therapy. Alternatively, a diagnostic 131-I scan and thyroglobulin measurement after TSH withdrawal had been used. In the last years recombinant TSH stimulation has been shown a sensitive way of thyroglobulin measurement without a break in the thyroid hormone replacement therapy. When TSH is rising, not only the iodine uptake will increase (which is favourable for the therapeutic application of iodine therapy), but also the thyroglobulin level increases - thus creating a sensitive way for dectection residual cancer tissue or metastases.
Recurrence of disease can be present as macroscopically proven tumour (with or without detectable thyroglobulin). However, also isolated biochemical tumour-activity can occur: a detectable thyroglobulin (after stimulation or during suppression therapy) without tumour localization. Recurrences are reported in series to be present between 5-15 % of the patients (3). There are several diagnostic procedures available to localize the source of thyroglobulin production including high dose 131-I, FDG-PET-scan, ultrasound or MRI scan of the neck and mediastinum and CT scan of the thorax. A high dose of I-131, can be given as treatment, but the post-therapeutic scan has also a diagnostic value, for -if the post-therapeutic scan is positive- the tumour can be localized and possible treated by surgery. However, if the post-therapeutic scan is negative this accounts for a less differentiated tumour with limited or no therapeutic options and often in a poor survival (4). The FDG-PET scan is a valuable alternative diagnostic option, with a higher sensitivity when the TSH level is elevated (5).
When metastases can be localized several treatment options are possible including I-131 therapy, surgery, embolization, radio-frequency ablation and external beam therapy. The overall survival of a patient with one recurrence is almost the same as the patients without recurrences. However, when multiple recurrences are present the survival decreases 30-40% (6). Chemotherapy has no value in the treatment of thyroid cancer. When persistent/recurrent disease is found, still a relatively long survival can be expected. Overall, differentiated thyroid cancer is a mostly curable cancer, with a number of treatment options. However, it is a rare disease, in which randomized trials for investigation for optimal diagnosis and treatment are scarce.

Why guidelines?
Although, there is a kind of consensus about the treatment of this cancer there are also many uncertainties. Treatment decisions are frequently based on local practice and experience.
Guidelines are necessary to support health care providers in improving quality of patient care.
They are based on systematic search and clinical appraisal of the literature and rigorous external review, in order to achieve consensus on statements including issues pertaining organization of care. Although differentiated thyroid cancer can be considered as a curable cancer, in Europe optimal life expectancy has not been reached. Teppo et al illustrated that there are large variations in 10-years overall survival of patients with thyroid cancer between the different countries, in men between 59 and 83% in women 72 and 88% (7).
An English survey (8) showed that a specialist setting (defined as a hospital with a multidisciplinary experienced team) was significantly better regarding adequate surgery, iodine therapy and the consequences of a high thyroglobulin.
The British Thyroid Association and the Royal College of Physicians were the first to develop guidelines based on Evidence Based Medicine (www.british-thyroid-association.org). Afterwards several consensus meetings and reports are organized based on expert opinion and available data (9, 10). Reaching a consensus with the experts in the field of thyroid cancer will support all workers in this field. However, it is necessary to realize that limited evidence is present for the different diagnostic and treatment strategies A great advantage of the development of guidelines in the individual countries is the focus on the local organization of care. For, even although the overall survival of thyroid cancer is good the disease free survival is remarkably lower. As was stated in the British Medical Journal: “Better management can improve survival in this curable cancer” (11).

The Dutch Thyroid Cancer Consensus Committee
The Dutch Thyroid Cancer Consensus Committee has been started in 2002 and was initiated by the Dutch Endocrinology Society and the Dutch Society of Nuclear Physicians. Representatives of all professional societies and the patient society in the field of thyroid cancer are participating and have been supported by the Dutch Institute of Healthcare Quality and the National Cancer Working Party.
Based on the bottlenecks and questions, that were contributed by the professional societies the literature was systematically searched and reviewed and classified the principles of Evidence Based Medicine. In Evidence Based Medicine several levels of evidence are present varying from randomized controlled trial to experts opinions (I-IV). This results in three grades of recommendations: A (Ia,Ib) based on at least one randomized controlled trial, B (IIa,IIb,III) when well conducted clinical studies are present, but no randomized clinical trial and C (IV) when a recommendation was based on expert committees.

A view from the Dutch consensus

Fine needle aspiration in thyroid nodules
Although the Fine Needle Aspiration (FNA) has its limitations regarding sensitivity and specificity, the sensitivity can be increased, when ultrasound is used. For that reason ultrasound guided aspiration has been advocated. Standardly/routinely description of thyroid nodules offers also the possibility to get familiar with ultrasound characteristics and to evaluate these characteristics in relation to the cytological findings.

Initial surgical approach
The prefered surgical approach to patients with lymph node metastases is a modified selective lymph node dissection and not the lymph node picking. Selective lymph node dissection results in a lower number of locoregional recurrences. However, to minize the complications (hypoparathyroidism, dysfynction of the bervus recurrence), it must be performed by an experienced surgeon.

Ultra-sound in follow-up
The serum thyroglobulin measurement can be used instead of the diagnostic 131-I scanning in the follow-up of low risk patients. The combination of thyroglobulin measurement during TSH stimulation and the ultrasound of the neck has a high sensitivity. Moreover, it is also possible to detect lymph node metastases in patients with undetectable thyroglobulin and negative diagnostic or therapeutic 131I scanning.

High risk and low risk groups
Prognostic scoring systems have been developed to apply the prognostic variables into clinical use. However, most of these systems have shortcomings, because they are based on retrospective follow-up data and so differences in treatment modalities are not considered in the evaluation of the initial prognostic factors. This accounts for differences in the results when the same prognostic system is applied to different series (12). In a comparative study the TMN system was the most reliable scoring system in predictability in the outcome of patients with thyroid carcinoma (13), and has been advocated as standard classification system for definition of tumour status.
The low risk group consists of patients between 20-45 years old, with papillary thyroid cancer T1-2 (except agressive histological variants like tall cell, columnar cell and diffuse sclerosering variant) or minimally invasive follicular thyroid cancer, without lymph-node and distant metastases, post-ablative thyroid uptake only in the thyroid bed, thyroglobulin level <1 ng/ml during TSH suppressive therapy 3 months after I 131 ablation and without the presence of Tg antibodies.

Follow-up strategy low risk patients
Withdrawal of thyroid hormone is the most specific way to measure thyroglobulin in the follow-up of patients with differentiated thyroid cancer. However, the yield of the available imaging techniques that have been used as gold standard is low. Alternatively, the TSH level can be increased by recombinant TSH, that has the advantage of continuing of the thyroid hormone therapy and prevention of hypothyroidism. Both follow-up strategies have been included in the guidelines, for the hypothyroidism during withdrawal is difficult for a number of patients.
The development and availability of ultrasensitive thyroglobulin assays makes TSH stimulation in the follow-up possibly redundant. However, the clinical value of low detectable thyroglobulin can only be judged in long-term follow up studies (14).

Follow-up strategy high risk patients
The follow-up in high risk patients cannot be standardized. Depending the individual clinical characteristics additional imaging techniques can be used, like ultrasound of the neck, FDG PET scanning and whole body iodine-131 scan (after a therapeutic high dosage).

Organization of the care for patients with differentiated thyroid cancer

The treatment of patients with thyroid cancer has to take place in a multidisciplinary team, consisting of internist-endocrinologist, surgeon, nuclear physician, pathologist, radiologist, radiotherapist and a specialized nurse and psychologist. Initial follow-up including thyroglobulin measurement and ultrasound of the neck after ablation therapy will be concentrated in the centers of iodine therapy.
In the next year the Dutch consensus will get finished and this can be considered as a starting-point for increasing multidisciplinary approach and strengthening of collaboration. For there are a number of controversial issues the next years can be used to develop multicenter trials for getting the answers. The text of these guidelines will be published on www.oncoline.nl.

Reference

1. Visser O, Brijnen J. Incidence of cancer in the Netherlands 1998: tenth report of the Netherlands cancer registry. Vereniging van Integrale Kankercentra: 2002.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA 2006; 295: 2164-7.
3. Links TP, Tol KM van, Jager PL, Plukker JT, Piers DA, Boezen HM, Dullaart RP, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. Endocr Relat Cancer 2005; 12: 273-80.
4. Tol KM van, Jager PL, Vries EG de, Piers DA, Boezen HM, Sluiter WJ, Dullaart RP, Links TP. Outcome in patients with differentiated thyroid cancer with negative diagnostic whole-body scanning and detectable stimulated thyroglobulin. Eur J Endocrinol 2003; 148: 589-96.
5. Tol KM van, Jager PL, Piers DA, Pruim J, Vries EG de, Dullaart RP, Links TP. Better yield of (18)fluorodeoxyglucose-positron emission tomography in patients with metastatic differentiated thyroid carcinoma during thyrotropin stimulation. Thyroid 2002; 12: 381-7.
6. Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, Pelizzo MR, Pezzullo L. Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg. 2004 Mar; 28 (3): 271-6.

7. Teppo L, Hakulinen T. Variation in survival of adult patients with thyroid cancer in Europe. Eur J Cancer 1998; 34: 2248-52.
8. Kumar H, Daykin J, Holder R, Watkinson JC, Sheppard MC, Franklyn JA. An audit of management of differentiated thyroid cancer in specialist and non-specialist clinic settings. Clin Endocrinol (Oxf) 2001; 54: 719-23.
9. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, et al. The American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006; 16: 109-42.
10. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154: 787-803.
11. Kendall-Taylor P. Managing differentiated thyroid cancer. Br Med J 2002; 324: 988-9.
12. Hannequin P, Liehn JC, Delisle MJ. Multifactorial analysis of survival in thyroid cancer. Pitfalls of applying the results of published studies to another population. Cancer 1986; 58: 1749-55.
13. Brierley JD, Panzarella T, Tsang RW, Gospodarowicz MK, O'Sullivan B. A comparison of different staging systems predictability of patient outcome. Thyroid carcinoma as an example. Cancer 1997; 79: 2414-23.
14. Persoon AC, Ouweland JM van den, Wilde J, Kema IP, Wolffenbuttel BH, Links TP. Clinical utility of an automated immunochemiluminometric thyroglobulin assay in differentiated thyroid carcinoma. Clin Chem 2006; 52: 686-91.

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Thyroglobulin (Tg) measurement used to monitor patients with differentiated thyroid carcinomas (DTC)

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Serum Tg measurements are primarily used as a tumor-marker for patients with DTC. It is critical that circulating Tg concentrations be interpreted relative to the pathology, surgical history and TSH status of the patient. Biases between methods preclude the use of different Tg or TgAb assays for the serial monitoring of patients. Recovery tests often fail to detect interfering TgAb. In the future, the use of more sensitive Tg assays (functional sensitivity <0.1 µg/L) should obviate the need for expensive rhTSH stimulation testing. Because the specificity of using an "undetectable" Tg as a risk factor for disease is inversely related to Tg assay sensitivity, in the future serial sensitive basal Tg monitoring without rhTSH stimulation will be used in conjunction with ultrasound. Both TgAb and HAMA interferences remain problems with IMA methodology. Because RIA methods appear resistant to these interferences, discordance between the IMA and RIA measurements made on a specimen is a useful way to detect interference.

Thyroglobulin (Tg) is the 660,000 Da precursor protein backbone for thyroid hormone biosynthesis and is co-secreted with thyroid hormones in response to TSH stimulation. Because Tg is derived uniquely from thyroid follicular cells, serum Tg measurement is primarily used as a tumor-marker for patients with differentiated thyroid cancers (DTC). Most thyroid tumors have the capability to synthesize and secrete Tg, although there may be considerable heterogeneity in the circulating Tg isoforms arising from neoplasms (1). Tg measurement is primarily made in serum, however Tg measured in the washout from fine-needle aspiration of suspicious lymph nodes is becoming an important adjunctive test to cytology (2).

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Variables influencing the interpretation of serum-Tg concentrations in DTC

A serum Tg elevation cannot be used to diagnose DTC because an elevated Tg is merely a non-specific indicator of the presence of thyroid pathology. It is only after a cytological/histological diagnosis has been made that serum Tg becomes a useful tumor marker for DTC. As summarized in figure 1, the Tg measured in the circulation reflects: 1) The mass of thyroid tissue present (the combined contribution from normal remnant tissue plus any tumor); 2) any thyroid injury, secondary to fine needle aspiration, surgery, radioiodine therapy or thyroiditis; and 3) the degree of TSH-receptor stimulation by endogenous or recombinant TSH, hCG (pregnancy) or TSH-receptor antibodies (TSAb) (present in Graves' hyperthyroidism).
As shown in figure 2, the Tg assay characteristics together with the patient's surgical history and TSH status can be used as benchmarks to interpret post-operative serum Tg concentrations (3). For example, using a Tg assay with functional sensitivity of 0.1