ABSTRACT: Background: Treatment guidelines for well-differentiated papillary thyroid carcinoma (PTC) are based on retrospective studies and vary among professional thyroid associations. Objectives: To evaluate physician adherence to guidelines, overall and by specialty. Methods: Questionnaires on the approach to low risk PTC were distributed among 51 surgeons and endocrinologists treating patients with PTC in tertiary medical centers. Results: A wide range of answers was recorded among physicians regarding the danger posed by low risk PTC to the patient's life, urgency with which treatment should be administered, type of treatment, and risks associated with this treatment. There was a significant between-group difference in treatment preference: endocrinologists chose total thyroidectomy with radioactive iodine, while surgeons favored hemithyroidectomy alone. Conclusions: There is a wide difference in treatment recommendations between treating physicians and different specialties with regard to low risk PTC. The wide variation within and between specialties may be explained by biases. KEY WORDS: guidelines, thyroid carcinoma, thyroidectomy, hemithyroidectomy, radioactive iodine

Advances in medical technologies and pharmaceuticals in recent years have provided physicians with a wide range of treatment choices. Each has advantages and disadvantages. Choosing the best treatment involves a complex process of weighing outcomes against side effects and risks as well as the effect that the choice will have on the quality of life. In their Nobel prize-winning studies, Kahneman and Tversky [1] showed that people tend to make mistakes when reaching decisions in uncertain conditions (such as more than one treatment option). They suggested that heuristics or biases programmed into human behavior may lead to intuitive reactions instead of a logically calculated mode of action. This is apparently true in medicine as well [2]. Physicians faced with more than one treatment option may select wrongly because of preexisting biases. To overcome these biases, physicians veer toward a reliance on evidence-based findings rather than intuition-based expert opinion. The evidence is also weighted according to the level of validity [3]. Thus, studies that represent expert opinion are valued less than studies that average data from large-scale clinical trials [4]. Although professional teams have written management guidelines using the relevant data published in the literature, studies have repeatedly shown that physicians do not always adhere to them [5]. There is evidence for over-utilization of some treatments, even if not very effective, and under-utilization of other, effective, ones [6]. This over- and under-use may be attributed to biases.

Although treatment decisions that diverge from professional guidelines may in some cases reflect conditions specific to the individual case in question, in other cases this diversion may reflect the physician's bias. Bias can also be the explanation for over- and under-use of some treatment modalities.

The evidence base for the treatment of low risk (early) papillary thyroid carcinoma is wide [7,8], but it is only level B, that is, derived from retrospective (not prospective) and uncontrolled studies. Analyzing the outcome in 42,686 patients with papillary carcinoma registered in the National Cancer Database, Hundahl et al. [7] showed that confined unifocal tumors measuring up to 4 cm have an excellent prognosis and 10 year survival rate (above 95%), and a low recurrence rate (< 10%)—regardless of the extent of surgery. At the same time, Blimoria et al. [8] reported a higher recurrence rate and lower survival in patients with tumors larger than 1 cm treated with hemithyroidectomy compared to total thyroidectomy (although the differences remained small for tumors up to 3 cm). Given the delicate equilibrium between the added advantages of total thyroidectomy against its added risk of greater morbidity, specific guidelines addressing the extent of surgery in patients with low risk tumors differ from country to country. Even within the United States, the National Comprehensive Cancer Network enables hemithyroidectomy for papillary carcinomas up to 4 cm in young patients with no other risk factors [9], and the American Thyroid Association does so only for tumors up to 1 cm [10]. Almost all other national guidelines enable hemithyroidectomy for tumors measuring 1 cm or less in a favorable host but do not rule out total thyroidectomy with adjuvant radioactive iodine treatment [10,11].
In this situation where guidelines allow for two treatment options, the present study evaluates physicians’ preference and evaluates differences between surgeons and endocrinologists. Possible factors that may influence treatment decisions are discussed.

PATIENTS AND METHODS

A six-item questionnaire evaluating the treatment options for low risk papillary thyroid carcinoma was administered to 51 physicians (15 surgeons and 36 endocrinologists) who regularly treat patients with thyroid cancer at tertiary medical centers. The participants were told that this was a survey to evaluate treatment choices, but not that the main focus was to identify inter-specialty differences. The following points were investigated and compared between the participating physicians:

- Physicians’ evaluation of the danger imposed by the disease on affected patients
- Urgency with which treatment should be administered
- The extent of treatment needed
- Morbidity associated with each of the possible treatments.

The different responses to each question were calculated for the whole group and for surgeons and endocrinologists separately. Fisher’s exact test (SPSS ver. 15 and WinPepi ver. 11.18) was used to compare the responses by medical specialty. Risk assessments were clustered into two groups, and 2 x 2 crosstabs were used to correlate risk assessments with treatment decisions. A P value < 0.05 was considered statistically significant.

RESULTS

The six items are:

- **Question 1** [Figure 1]: To what extent does low risk papillary carcinoma jeopardize patient health?
  Question 1 was graded on a scale from 1 (lowest threat) to 5 (highest). The responses of the study sample were characterized by a wide variation. Nine physicians considered low risk papillary carcinoma of the thyroid a grade 1 threat while three physicians considered it a grade 5 threat. There was no significant difference in responses between surgeons and endocrinologists.

- **Question 2** [Figure 2]: How urgently should treatment be administered in low risk papillary carcinoma?
  This question was graded on a 5 point scale, similar to question 1, with a similarly wide distribution of responses and no significant difference by medical specialty.

- **Question 3** [Figure 2]: What would be your therapeutic approach to a 40 year old woman with an incidental finding of a 10 mm thyroid nodule shown to be papillary carcinoma by fine-needle aspiration?
  All the surgeons chose hemithyroidectomy as the treatment of choice, whereas the endocrinologists were split, with 15 advocating hemithyroidectomy and 21 total thyroidectomy. The difference between the physician groups was statistically significant (P < 0.001).

- **Question 4** [Figure 2]: Is adjuvant radioactive iodine treatment necessary if the pathological examination reveals a single 10 mm focus with no extra-thyroid extension and ultrasound showing no lymphadenopathy?
  The range of answers was wide. Although all surgeons voted for hemithyroidectomy, some advocated radioiodine adjuvant treatment when specifically asked. There was no statistically significant difference between surgeons and endocrinologists.

- **Question 5** [Figure 3]: What is the surgical risk of total thyroidectomy vs. hemithyroidectomy?

- **Question 6** [Figure 3]: To what degree does radioactive iodine treatment decrease quality of life?
For question 5, physicians were asked to choose between two possible answers: “Total thyroidectomy has double the risk of hemithyroidectomy” or “Total thyroidectomy has a slightly higher risk than hemithyroidectomy.” For question 6, physicians rated the decrease they would expect in patients’ quality of life on a scale of 1 to 5. Similar to questions 1–4, there was wide variability in responses, with no significant difference by medical specialty.

Figure 4 shows the correlation between evaluations of the tumor-associated risk and choice of treatment. No correlation was found between the responses to question 1 (gravity of the disease) and question 3 (extent of recommended treatment). There was a trend toward significance in the relationship between question 5 (surgical risk associated with total thyroidectomy) and choice of treatment, with more physicians who regard total thyroidectomy as affecting quality of life recommending hemithyroidectomy ($P = 0.08$). Similarly, more physicians who thought radioactive iodine was associated with low morbidity recommended treatment with adjuvant radioactive iodine ($P = 0.051$).

**DISCUSSION**

Decision making in many areas, including medicine [6], is influenced by biases. In order to help physicians make the right treatment decision and overcome personal biases, guidelines (determined by experts and based on high volume data) have been published. Nonetheless, repeated studies show that physicians often fail to adhere to written guidelines [5].

The present study sought to: a) determine if physicians who encounter patients with papillary cancer on a daily basis are uniform in their attitudes and treatment choices for patients with low grade papillary carcinoma, and b) evaluate differences between surgeons and endocrinologists. In the absence of prospective double-blind controlled studies the preferred extent of surgery for low risk papillary carcinomas remains unclear. Current treatment guidelines are based on large-scale multicenter retrospective studies [8-11] and allow for a wide range of treatment options from hemithyroidectomy to total thyroidectomy with adjuvant radioactive iodine.

Data for the present study were derived from a six-item questionnaire distributed to 51 physicians treating patients...
For a 10 mm papillary carcinoma in the absence of other compromising factors, there was a clear difference by medical specialty in the recommended treatment, with endocrinologists preferring total thyroidectomy and surgeons hemithyroidec-
tomy. Although both the NCCN and ATA as well as many of the European guidelines allow for hemithyroidec-
tomy in these cases [10,11], half the endocrinologists opted for a more radical solution. Furthermore, the lack of correlation between the responses regarding gravity of the disease and its treatment indicates that physicians who thought papillary thyroid carcinoma was a considerable threat to the patient did not necessarily opt for more extensive treatment. Physicians who opted for more extensive treatment did not necessarily believe papillary thyroid carcinoma was a considerable threat.

The concept of “risk aversion,” developed by Kahneman and Tversky [12], suggests that people strongly prefer avoiding losses to acquiring gains and that the appreciation of losses is twice as powerful as the appreciation of gains. As such, risk aversion may induce the overuse of radical measures to avoid loss. Accordingly, the choice of radical treatment by the endocrinologists may have been prompted by the fear of loss (life) associated with treating a cancer patient. At the same time, the choice of less radical treatment by the surgeons may have been prompted by a fear of loss (morbidity) that can accompany total thyroidectomy. Many studies in the field of economics show that intuition and past experience play a greater role in decision making than analytical assessment [12].

Physicians, surgeons and endocrinologists alike are exposed to the same published medical data. Still, they present wide variations in their attitude and treatment recommendations, thus reflecting possible influences or bias on the physicians’ professional practice and treatment recommendations. This has to be taken into consideration and corrected. A mathematical model may be a useful instrument to overcome these shortcomings.

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Correspondence
Dr. R. Feinmesser
Dept. of Otorhinolaryngology and Head and Neck Surgery, Rabin Medical Center (Beilinson Campus), Petah Tikva 49100, Israel
Phone: (972-3) 937-6451
Fax: (972-3) 937-6467
e-mail: fein6@walla.co.il

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NCCN = National Comprehensive Cancer Network
ATA = American Thyroid Association


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**Capsule**

**A vaccine targeting mutant IDH1 induces antitumor immunity**

Mononucleic point mutations of isocitrate dehydrogenase type 1 (IDH1) are an early and defining event in the development of a subgroup of gliomas and types of tumor. They almost uniformly occur in the critical arginine residue (Arg132) in the catalytic pocket, resulting in a neomorphic enzymatic function, production of the oncometabolite 2-hydroxyglutarate (2-HG) genomic hypermethylation, genetic instability and malignant transformation. More than 70% of diffuse grade II and grade III gliomas carry the most frequent mutation, IDH1(R132H). From an immunological perspective, IDH1(R132H) represents a potential target for immunotherapy as it is a tumor-specific potential neoantigen with high uniformity and penetrance expressed in all tumor cells. Schumacher et al. demonstrate that IDH1(R132H) contains an immunogenic epitope suitable for mutation-specific vaccination. Peptides encompassing the mutated region are presented on major histocompatibility complexes (MHC) class II and induce mutation-specific CD4+ T-helper-1 (TH1) responses. CD4+ TH1 cells and antibodies spontaneously occurring in patients with IDH1(R132H)-mutated gliomas specifically recognize IDH1(R132H). Peptide vaccination of mice devoid of mouse MHC and transgenic for human MHC class I and II with IDH1(R132H)p123-142 results in an effective MHC class II-restricted mutation-specific antitumor immune response and control of pre-established syngeneic IDH1(R132H)-expressing tumors in a CD4+ T cell-dependent manner. As IDH1(R132H) is present in all tumor cells of these slow-growing gliomas, a mutation-specific anti-IDH1(R132H) vaccine may represent a viable novel therapeutic strategy for IDH1(R132H)-mutated tumors.

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Eitan Israeli

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**Capsule**

**Putative cis-regulatory drivers in colorectal cancer**

The cis-regulatory effects responsible for cancer development have not been as extensively studied as the perturbations of the protein coding genome in tumorigenesis. To better characterize colorectal cancer (CRC) development Ongen et al. conducted an RNA-sequencing experiment of 103 matched tumor and normal colon mucosa samples from Danish CRC patients, 90 of which were germline-genotyped. By investigating allele-specific expression (ASE) the authors show that the germline genotypes remain important determinants of allelic gene expression in tumors. Using the changes in ASE in matched pairs of samples they discovered 71 genes with excess of somatic cis-regulatory effects in CRC, suggesting a cancer driver role. The authors correlated genotypes and gene expression to identify expression quantitative trait loci (eQTLs) and found 1693 and 948 eQTLs in normal samples and tumors, respectively. They estimate that 36% of the tumor eQTLs are exclusive to CRC and show that this specificity is partially driven by increased expression of specific transcription factors and changes in methylation patterns. They also show that tumor-specific eQTLs are more enriched for low CRC genome-wide association study (GWAS) P values than shared eQTLs, which suggests that some of the GWAS variants are tumor-specific regulatory variants. Importantly, tumor-specific eQTL genes also accumulate more somatic mutations when compared to the shared eQTL genes, raising the possibility that they constitute germline-derived cancer regulatory drivers. Collectively the integration of genome and the transcriptome reveals a substantial number of putative somatic and germline cis-regulatory cancer changes that may have a role in tumorigenesis.

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Eitan Israeli