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Original Scientific Paper

DOES THE PRESENCE OF CHRONIC LYMPHOCYTIC THYROIDITIS AFFECT DIAGNOSTIC VALUE OF FINE NEEDLE ASPIRATION BIOPSY IN BETHESDA CATEGORY III NODULES?

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SUMMARY – This study aimed to determine the relationship between the presence of Hashimoto's thyroiditis (HT) and malignancy rates with prognostic factors in thyroid nodules diagnosed as Bethesda category III, and to examine the effect of HT on diagnostic value of fine-needle aspiration biopsy (FNAB). Demographic information, preoperative examination, and final pathological evaluation of patients with Bethesda category III (AUS-FLUS) nodules who had been operated on in our department over the last 6 years were analyzed. Statistical analyses were performed using the Student's t-test, Mann-Whitney U test and χ^2-test and logistic regression analysis using SPSS version 22 software. The malignancy rate on final pathology of 159 patients was 24.5%. Malignancy rates were found to be higher in patients with HT coexistence (30.7% *vs.* 21.5%, p=0.20). Poor prognostic factors such as multifocality, number of metastatic lymph nodes (p=0.04), and extrathyroidal extension were more common in patients with cancer in the pathology specimen who were in the non-HT group. It cannot be said that HT decreases diagnostic value of FNAB in lesions diagnosed with AUS-FLUS. The lower incidence of poor prognostic factors in the HT group may be attributed to cytotoxic cell dominance in tumor immunity.

Key words: *Carcinogenesis; Endocrine surgery; Immunology; Pathomorphological diagnosis of tumors; Prognostic factors*

Introduction

Today, fine needle aspiration biopsy (FNAB) is accepted as the gold standard in the evaluation of suspicious thyroid nodules. The Bethesda system, which was first published in 2010, is used on reporting cytopathological examinations. Bethesda category III nodules, which are named as "atypia of undetermined significance-follicular lesions of undetermined significance" (AUS-FLUS), carry a malignant potential at rates varying between 6% and 48% (average 16%), as stated in the 2015 guidelines of the American Thyroid Association (ATA)[1]. There are publications arguing that this rate is higher in cases that were operated on without follow-up or additional examinations[2]. Bethesda category III nodules, which are considered as an intermediate cytology, leave clinicians in a dilemma on making surgical decision. In the ATA 2015 guidelines, there are additional examinations such as repetition of FNAB and molecular examinations for Bethesda category III lesions, and follow-up or surgical recommendations varying according to the ultrasonographic characteristics of the nodule[3].

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Hashimoto's thyroiditis (HT), known as chronic lymphocytic thyroiditis, was described by Hakaru Hashimoto in 1912. It has been understood that the disease is a process that begins with triggering of CD4 T-helper cells, and both humoral and cellular immunity drive thyroid follicular cells to apoptosis. Although HT, which affects almost 2% of the world population and is the most common cause of hypothyroidism in Western societies, mostly affects women aged 30-50 years (ratio of 1:10 to 1:20), in their article published in 2022 Jukić *et al*. emphasized the importance of screening older women for subclinical hypothyroidism[4]. According to the literature, thromboembolism due to thyroid hormone elevation in the early stages of HT and permanent hypothyroidism due to iodine-containing drug use in the late stages may be observed[5,6]. What is more worrying is that the prevalence of papillary thyroid cancer (PTC) associated with HT has increased threefold compared to other thyroid diseases, as reported by Dailey *et al*.[7]. Mulder *et al*. argue that it has been easier to make a diagnosis of nodule AUS due to cellular atypia seen in HT and this situation negatively affects diagnostic value of FNAB[2]. In our study, we aimed to examine the effect of HT presence on surgical or follow-up decisions in patients with nodules diagnosed with AUS-FLUS through FNAB and diagnostic value of FNAB in these patients.

Patients and Methods

A total of 159 patients who had nodules in AUS-FLUS cytology among 995 patients who underwent thyroidectomy between February 2014 and December 2019 in our department were included in our retrospective study. The patients were subjected to preoperative ultrasonographic evaluation by experienced radiologists, and findings of aspiration biopsies obtained from nodules of suspicious appearance were reported in accordance with the Bethesda system. There were 135 patients that underwent bilateral total thyroidectomy and 24 patients underwent lobectomy. Demographic characteristics, preoperative ultrasonography, thyroid scintigraphy, and postoperative pathology reports of the patients were analyzed. Properties of the nodules such as echogenicity, calcification, presence of halo, and scintigraphic activity were evaluated.

The diagnosis of HT was made by final pathological examination of resection specimens. HT was present in 52 (32.7%) of 159 patients included in the study (group 1). Group 2 included 107 patients without HT. Demographic differences, benign and malignant lesions in preoperative imaging examinations, and thyroidectomy specimens were compared between these two groups. The number of tumor foci, presence of extrathyroidal extension, status of lymphovascular-perineural invasion, and number of dissected metastatic lymph nodes were evaluated in cases with a malignant diagnosis.

Statistics

The SPSS version 22 software was used on statistical analysis. Continuous data with normal distribution were evaluated with Student's t-test, while Mann Whitney-U test and χ^2-test, and logistic regression analysis were used for nonparametric data.

Results

Of the 159 patients included in the study, 33 (20.7%) were male and 126 (79.3%) were female. Their mean age was 48 (21-74) years and mean nodule diameter was 25 (5-86) mm. In 15% of the patients, the size of the dominant nodule was 1 cm or less. The number of patients who had two biopsies on the same nodule was 93 (58%).

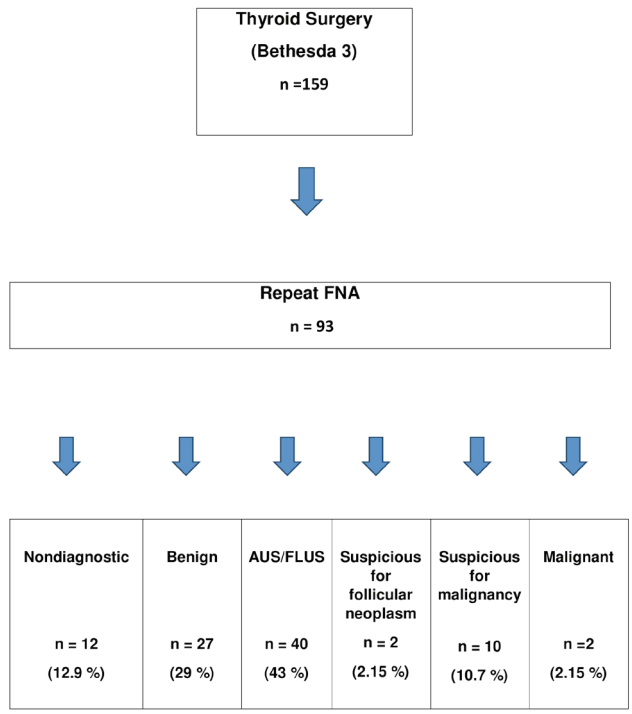

Fig. 1. Repeated fine needle aspiration biopsy results of Bethesda category III nodules.

The results of the 93 patients who underwent repeat FNAB were as follows: nondiagnostic in 12, benign in 27, AUS-FLUS in 40, suspected follicular neoplasia in 3, suspicious malignancies in 10, and papillary cancer in 2 nodules. Thus, the rate of making the same diagnosis in second biopsy of the nodules reported as AUS-FLUS was 43% (40/93) (Fig. 1). Of the 159 patients who had surgery, definitive pathology was reported as benign for 120 nodules. Although adenomatous hyperplasia was the most frequently diagnosed lesion, Hürthle cell adenoma, nodular goiter and non-invasive follicular thyroid neoplasm with papillarylike nuclear features (NIFTP) were seen as other benign and borderline outcomes. Incidental (extranodal) cancer focus was observed in 5 specimens among these 120 patients.

The classic variant of papillary cancer was the most commonly diagnosed malignant lesion in our study. The rates of cancer types seen in Bethesda category III nodules are summarized in Figure 2.

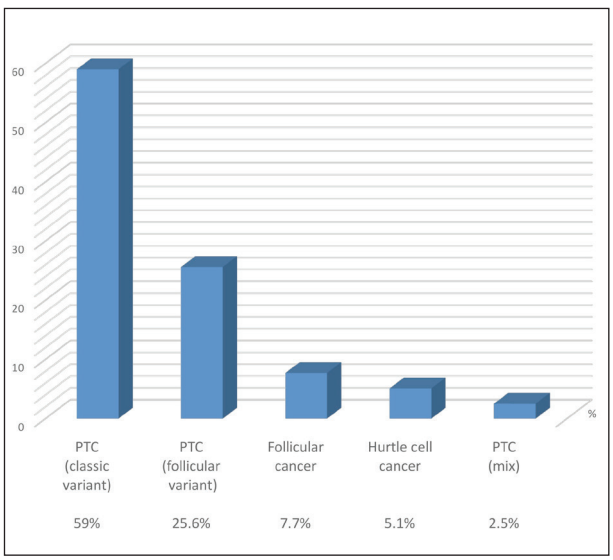

Fig. 2. The rates of cancer types seen in Bethesda category III nodules.

While the malignancy rate of 159 nodules diagnosed with AUS-FLUS included in the study was 24.52% (39/159), the rate was 30.76% (16/52) in the group with HT and 21.49% (23/107) in patients without HT. Although the rate of malignancy was high in patients with HT, it was not statistically significant (p=0.20) (Fig. 3).

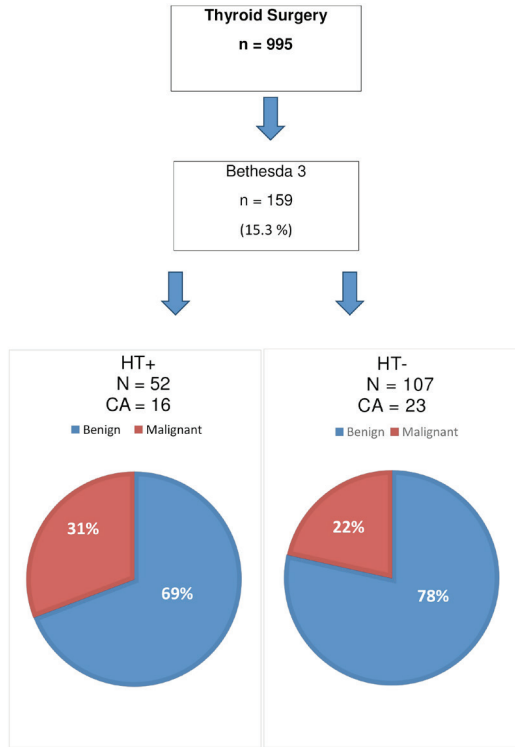

Fig. 3. Distribution of malignancy rates according to the presence of Hashimoto's thyroiditis.

The variability in the incidence of malignancy in the presence of HT according to the results of second FNAB is shown in Table 1. The malignancy rate was 33.3% and 28% in patients with and without HT who were diagnosed with AUS-FLUS in both biopsies, respectively. It was observed that the presence of HT did not make a significant difference in malignancy rate as a result of FNAB. Although the rate of second FNAB results in patients with HT was higher than in patients without HT, the difference was not significant (28.8% *vs*. 23.4%).

In our study, it was observed that HT, which is more common in normal population in the ages of 30-50, was not age-related in surgical patients. The presence of HT was found to be significantly higher in female patients (p=0.01). Hypoechogenicity of the nodule on ultrasonography, presence of microcalcification, presence of halo, hypoactivity in thyroid scintigraphy, and lymphovascular invasion rates in malignant lesions did not exhibit a statistically significant difference with HT. The extrathyroidal extension was observed in 17.6% (3/17) of cases in the presence of HT, while this rate was 40.7% (11/27) in cancers without HT.

Table 1. Relationship between HT presence and FNA results

Repeat FNA result	HT+ (malignancy rate)	HT- (malignancy rate)	Total
No repeat FNA	4/20 (20%)	8/46 (17.4%)	66
Nondiagnostic	2/4 (50%)	0/8 (0%)	12
Benign	2/9 (22.2%)	3/18 (16.6%)	27
AUS-FLUS	5/15 (33.3%)	7/25 (28%)	40
Suspicious for follicular neoplasm		1/2 (50%)	2
Suspicious for malignancy	2/3 (66.6%)	3/7 (42.8%)	10
Malignant	1/1 (100%)	1/1 (100%)	2
Total	16/52 (30.7%)	23/107 (21.5%)	159 (p=0.2)

HT = Hashimoto's thyroiditis; FNA = fine needle aspiration; AUS-FLUS = atypia of undetermined significance-follicular lesions of undetermined significance

Table 2. Relationship between the presence of HT and variables

Variable	HT+	HT-	Total	p value
Age	48.4±11	49±10.9	48.8±10.9	0.77
Male gender	15.2%	84.8%	n=33	**0.016**
Female gender	37.3%	67.2%	n=126	**0.016**
Nodule diameter	22±13	26.2±15	24.9±14.5	0.09
Ultrasonic hypoechogenicity	64.4%	56.3%	59%	0.66
Microcalcification	54.5%	51.7%	52.5%	0.80
Halo	53.6%	60.6%	57.4%	0.58
Scintigraphic hypoactivity	88.9%	91.3%	90.6%	0.64
Number of tumor foci	1.4	1.7	1.6	0.18
Metastatic lymph nodes	0.41±1.2	1.65±4.1	1.08±3.16	**0.04**
Extrathyroidal extension	17.6%	40.7%	31.8%	0.10
Lymphovascular invasion	5.9%	22.2%	15.9%	0.22

HT = Hashimoto's thyroiditis

In 50% (8/16) of the cancers detected in the presence of HT, the focus was 1 cm or less, while this rate was 13% (3/23) in cases without HT. Examining the rates of cancer foci, it was calculated that the rate of unifocal malignancies was 81.3% (13/16) in the presence of HT and 56.5% (13/23) in cases without the presence of HT. Besides, it was found that the number of metastatic lymph nodes was significantly lower in HT presence (p=0.04). These findings suggest that thyroid malignancies with HT in pathology specimens had fewer poor prognostic criteria. The correlation between HT and demographic parameters, ultrasonographic-scintigraphic features, and tumor characteristics are summarized in Table 2.

There was no correlation between ultrasonographic imaging of microcalcification in the nodule and presence of HT; however, it was shown that microcalcification in the nodule was statistically more significant in predicting malignancy in the presence of HT (p=0.001). Male gender was more prominent than female gender in terms of malignancy rates in nodules diagnosed with AUS-FLUS (33% *vs*. 22%). The rate of malignancy, which was found to be 25% in female patients in the presence of HT, reached 80% in male patients (p=0.01). When the factors predicting malignancy were examined in 159 patients whose first biopsies were presented as AUS-FLUS, although there were factors such as the presence of AUS-FLUS in both biopsies, the presence of HT, male gender, nodule size below 1 cm, and microcalcification in the nodule were effective in univariate analysis. Only two factors, a nodule size below 1 cm (p=0.04) and microcalcification in the nodule (p=0.02), were found to be statistically significant in predicting malignancy when examined at 95% confidence interval in logistic regression analysis.

Discussion

The decrease in T regulatory (T Reg) cells shown in HT, resulting in an increase in Th1 and NK cell proliferation, leads to chronic inflammation and thus

Table 3. Association of HT and thyroid cancer

Authors	Number of patients	Cancer with HT, n (%)
Dailey *et al.*[7]	278 PTC	35 (12.6%)
Singh *et al.*[15]	388 PTC	57 (15%)
Chesky *et al.*[16]	432 HT	48 (11.1%)
Ott *et al.*[17]	161 TC	61 (38%)
Eisenberg *et al.*[18]	120 TC	13 (10.8%)
Sclafani *et al.*[19]	48 HT	8 (17%)
Schäffler *et al.*[20]	153 TC	10 (6.5%)
Mateša-Anić *et al.*[21]	10508 FNA	42 (0.5%)
Cipolla *et al.*[22]	71 PTC	19 (26.7%)
Pisanu *et al.*[23]	344 PTC	33 (9.6%)
Kebebew *et al.*[24]	136 PTC	41 (30%)
Matsubayashi *et al.*[25]	95 PTC	36 (37.9%)
Yoon *et al.*[26]	195 PTC	56 (28.7%)
Paulson *et al.*[27]	139 PTC	61 (43.8%)
Repplinger *et al.*[28]	217 HT	63 (29%)

HT = Hashimoto's thyroiditis; PTC = papillary thyroid cancer; TC = thyroid cancer; FNA = fine needle aspiration

carcinogenesis. It is also thought that this cytotoxic cell dominance has positive effects on PTC prognosis. In their 2014 study, Paparodis *et al*. conclude that tumor-infiltrating lymphocytes in PTC are a heterogeneous group and that DN T lymphocytes (CD4-, CD8-) that particularly suppress immunity are one of the dominant mechanisms in papillary thyroid cancer. They also demonstrated the effectiveness of the immunosuppressive FoxP3 gene on PTC patients[8]. Similarly, in another study, it has been shown that the effectiveness of the FoxP3 gene is reduced in HT[9]. Crispin *et al*. emphasize the importance of Th1 cells, which have become dominant in the mechanism of HT formation, suggesting that immune T regulatory (T Reg) lymphocytes, which are commonly detected in PTC, are rarely seen in HT[10]. In another article, it has been shown that there is a positive correlation between the ratio of T Reg infiltrating PTC cells and cancer stage[11].

The Bethesda system has made a breakthrough in the cytopathological evaluation of thyroid nodules with its standards. There are publications reporting AUS-FLUS rate of 12%, which was previously accepted as 7%[3]. In our study, the patients who were followed-up were excluded from the scope of the study, so there are not enough data about the rate of AUS-FLUS reporting as a result of FNAB. The American Association of Clinical Endocrinologists (AACE) and the European Thyroid Association (ETA) preferred to collect Bethesda category 3 and category 4 lesions under a single heading[12]. Although Bethesda category 3 lesions leave clinicians in a dilemma in the decision whether to follow-up or conduct surgery, Shi *et al*. observed that the exclusion of this category from the classification significantly increased false positive and false negative results[13]. Therefore, the management of Bethesda category 3 lesions appears to be the main problem in decision-making. Although the average malignancy rates of these lesions are stated as 16% in the ATA guidelines, most authors state that these rates are widely distributed when the subgroups of the patients included in the study are considered. For example, classifying the Bethesda category 3 lesions according to their ultrasonographic features, Ho *et al*. found a malignancy rate between 7% and 56%. Again, in the same article, it is mentioned that a malignancy rate of 38% was detected in nodules diagnosed with AUS-FLUS through FNAB and operated without any other evaluation. It is known that the rates of malignancy change when evaluated separately as those who underwent repeated biopsy, who were followed up without requiring additional examination, and those who were planned for surgery as a result of additional examinations[14]. As it is not possible to operate all patients with Bethesda category III nodules, it has so far not been possible to determine a clear malignancy rate. The patients included in our retrospective study consisted of those who were operated immediately after the diagnosis of AUS-FLUS and those who were operated after being subjected to additional examinations or after a certain period of follow-up. The malignancy rate was 24.5% in the patients.

The association between HT and papillary cancer of the thyroid has been known since the article of Dailey *et al.* published in 1955. Singh *et al.* report that the prevalence of papillary cancer in patients with HT was 2.8 times higher[15]. When looking at the studies in the literature, the incidence of PTC in the presence of HT varies between 8% and 63%. Some of these studies are summarized in Table 3[7,15-28]. In our study, the rate of malignancy in the group with HT was found to be higher than the group without HT (30.8% *vs*. 21.5%), but this was not considered statistically significant. In patients with HT, the rate of reporting the second FNAB result as AUS-FLUS is higher than that of the group without HT (28.8% *vs*. 23.4%). It is observed that the presence of HT increases the diagnosis of AUS-FLUS in FNAB, but also causes an increase in malignancy due to chronic inflammation.

Mulder *et al*. divided 293 patients with AUS-FLUS cytology, who were operated on between 2009 and 2018 for thyroid nodules, into two groups, i.e., those with HT and those without HT, and found malignancy rates of 44% and 60% in these groups, respectively. This situation was explained by the fact that cellular atypia developing due to HT suggested AUS-FLUS diagnosis for non-malignant nodules and negatively affected diagnostic value of FNAB[2]. It is possible to come across literature articles indicating that a group of diseases including HT may increase false positivity even in noninvasive diagnostic tools such as scintigraphy scan with technetium-99m (sestamibi)[29]. In the article by Ho *et al*., the rate of malignancy has been reported as 38.6% (135/350) even in patients who were urgently operated on because they were diagnosed with AUS-FLUS and had suspicious features[14]. We attribute the low malignancy rate of 24.5% in our

study compared to the general literature to the preference of surgical treatment in patients whose follow-up was difficult due to socioeconomic conditions, and an increase in the number of surgeries in patients with multi-nodular goiter, which is frequently encountered in endemic regions with iodine deficiency. The malignancy rates of nodules diagnosed with AUS-FLUS for the second time were found to be higher in patients with HT. Similarly, it was seen that despite the small number of cases, malignancy rates were higher in nodules belonging to other Bethesda categories as a result of second biopsy, in the presence of HT. This situation can be interpreted in a way that chronic inflammation due to autoimmunity causes an increase in malignancy rates independent of the Bethesda category. The prevalence of HT in female patients was found to be statistically significant, in accordance with the literature[30]. Again, as Zhu *et al*. stated in their cohort study, the number of metastatic lymph nodes was significantly less in patients with HT[31]. Tumor diameter, which is one of the poor prognostic factors, was found to be less in patients with HT, in line with the literature[32,33]. The opinion stated by some authors that there is no relationship between biological behavior of PTC and HT has led to the interpretation that this issue has not been clarified[34,35]. According to Liang *et al*., multifocality was more common in patients with HT in PTC[32]; however, in our study, the situation was quite opposite. Although poor prognostic factors (multifocality, large tumor diameter, extrathyroidal extension, lymphovascular invasion, suspicious scintigraphic and ultrasonographic features) were more common in the group without HT, this was not found to be statistically significant in our study, except for the number of metastatic lymph nodes.

In conclusion, our study associated the higher rate of malignancy in patients with nodules diagnosed with AUS-FLUS with HT with carcinogenesis due to chronic inflammation. However, at the same time, we interpret the lower incidence of negative prognostic factors such as tumor size, multifocality, extrathyroidal extension, and number of metastatic lymph nodes in PTC patients with HT as being due to a decreased T Reg ratio and increased cytotoxic cell activity suppressing aggressive biological characteristics of the tumor. We believe that in Bethesda category III lesions accompanied by HT, surgery should be prioritized in the treatment algorithm, especially in male patients.

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Sažetak

UTJEČE LI PRISUTNOST KRONIČNOG LIMFOCITNOG TIREOIDITISA NA DIJAGNOSTIČKU VRIJEDNOST TANKOIGLENE ASPIRACIJSKE BIOPSIJE KOD ČVOROVA KATEGORIJE BETHESDA III?

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Cilj ove studije bio je utvrditi vezu između prisutnosti Hashimotova tireoiditisa (HT) i stope malignosti s prognostičkim čimbenicima u čvorovima štitnjače s dijagnozom Bethesda kategorije III. te ispitati učinak HT-a na dijagnostičku vrijednost aspiracijske biopsije tankom iglom (FNAB). Analizirani su prijeoperacijski pregledi i završne patološke procjene bolesnika s čvorovima Bethesda kategorije III. (AUS-FLUS) koji su operirani posljednjih 6 godina. Statističke analize provedene su pomoću Studentova t-testa, Mann-Whitneyeva U testa i χ^2-testa te logističke analize primjenom programa SPSS 22. Stopa malignosti u konačnoj patologiji 159 bolesnika bila je 24,5%. Utvrđeno je da su stope malignosti veće u bolesnika s istodobno prisutnim HT-om (30,7% naspram 21,5% p=0,20). Loši prognostički čimbenici poput multifokalnosti, broja metastatskih limfnih čvorova (p=0,04) i ekstratireoidnog širenja bili su češći u bolesnika s karcinomom u patološkom uzorku koji su bili u skupini bez HT-a. Ne može se tvrditi da HT smanjuje dijagnostičku vrijednost FNAB-a u lezijama s dijagnozom AUS-FLUS. Niža učestalost loših prognostičkih čimbenika u skupini s HT-om može se pripisati dominaciji citotoksičnih stanica u imunosti tumora.

Ključne riječi: *Karcinogeneza; Endokrina kirurgija; Imunologija; Patomorfološka dijagnostika tumora; Prognostički čimbenici*