

1 **DİFERANSİYE TİROİD KARSİNOMLARINDA ABLASYON**
2 **KONTROLÜ SIRASINDA ORTAYA ÇIKAN 5 mCi İYOT-131**
3 **SİNTİGRAFİSİ NEGATİF, TİROGLOBULİN POZİTİF**
4 **UYUMSUZLUĞUNUN DEĞERLENDİRİLMESİ**

5
6 **ÖZET**

7 **Amaç:** Diferansiye tiroid karsinomu (DTK) nedeniyle opere edilmiş ve ablasyon amacıyla
8 yüksek doz radyoaktif iyot (RAİ) verilmiş hastalarda, ablasyon kontrolü sırasında ortaya
9 çıkan 5 mCi (185 MBq) İyot-131 tüm vücut sintigrafisi (TVS) ve tiroglobülin (Tg) değeri
10 uyumsuzluğunu ve bunun olası nedenlerini incelemeyi amaçladık.

11 **Hastalar ve Yöntem:** Çalışmamızda 1992-2009 yılları arasında DTK tanısı ile RAİ tedavisi
12 verilen, ablasyon kontrolü için yapılan 5 mCi (185 MBq)-TVS (-) ve Tg değeri ≥ 2 ng/ml olan
13 36 hasta retrospektif olarak incelendi ve hasta grubunu oluşturdu. Tg değerleri < 2 ng/ml olan
14 ve uyumsuzluk bulunmayan 36 hasta ise kontrol grubu olarak alındı. Hasta ve kontrol
15 grubunun karşılaştırılmasında yaş, cinsiyet, histopatolojik özellikler, ablasyon dozu, ablasyon
16 öncesi Tg değeri ve ablasyon esnasındaki 24. saat RAİ uptake değeri kullanıldı. Ayrıca hasta
17 grubu da uyumsuzluk nedeni açısından incelendi.

18 **Bulgular:** Hasta grubunda 28 K, 8 E, yaş ort: 45.6 ± 11.39 ; kontrol grubunda 29 K, 7 E , yaş
19 ort: 41.5 ± 11.69 idi. Hasta grubunda uyumsuzluk nedenine yönelik yapılan tetkikler
20 sonucunda 15 (%42) hastada (9 K, 6 E, yaş ort: 50.66 ± 10.73) lenf bezi metastazı saptanırken
21 (lenf nodu grubu), 21 (%58) hastada (19 K, 2 E, yaş ort: 41.5 ± 10.44) uyumsuzluk nedeni
22 bulunamadı (mikrometastatik grup).

23 Yapılan istatistiksel çalışmada, hasta ve kontrol grupları arasında yumuşak doku invazyonu
24 ($p < 0.003$), ablasyon öncesi Tg değeri ($p < 0.002$) ve tümör çapı > 2 cm ($p < 0.035$) açısından
25 anlamlı fark bulundu. Hasta grubundaki lenf nodu varlığına göre yapılan değerlendirmede
26 ise, E cinsiyet ($p < 0.03$), tümör çapı > 2 cm ($p < 0.05$), tiroid kapsül invazyonu ($p < 0.03$) ve

27 yaş>40 (p<0.01) gibi parametrelerin karşılaştırılmasında lenf nodu ve mikrometastatik grup
28 arasında anlamlı fark bulundu.

29 **Sonuç:** Ablasyon kontrolü sırasında ortaya çıkan 5 mCi-TVS (-), Tg (+) uyumsuzluğunda
30 tespit edilebilen başlıca neden lenf nodu metastazıdır.

31 **Anahtar Kelimeler:** Diferansiye tiroid karsinomu, radyoaktif iyot tedavisi, I-131 tüm vücut
32 tarama, lenf nodu metastazı

33

34

35 **EVALUATION OF DIFFERENTIATED THYROID CANCER**
36 **PATIENTS WHOSE RADIOIODINE SCANS ARE NEGATIVE,**
37 **THYROGLOBULIN VALUES ARE POSITIVE AT THE ABLATION**
38 **OUTCOME CONTROL**

39

40 **ABSTRACT**

41 **Objectives:** We aimed to evaluate the discordance of 5 mCi (185 MBq) I-131 whole body
42 scan (WBS) and thyroglobulin (Tg) values at the ablation outcome control in differentiated
43 thyroid cancer (DTC) patients who had thyroidectomy and then received radioiodine (RAI)
44 ablation.

45 **Patients and Methods:** We evaluated 36 DTC patients retrospectively who had RAI
46 treatment in our department between 1992-2009 and whose 5 mCi (185 MBq) I-131 WBS
47 were negative, but Tg values were ≥ 2 ng/ml during ablation outcome control (Patient group).
48 36 patients whose Tg values were < 2 ng/ml and showed no discordance at the similar
49 occasion made up the control group. Patient and control groups were compared in terms of
50 age, gender, histopathological features, ablation dose, Tg value before ablation, and 24. hour
51 RAI uptake value during ablation. The patient group was then evaluated for the cause of
52 discordance.

53 **Results:** There were 28 female, 8 male patients whose mean age was 45.6 ± 11.39 in patient
54 group. In control group, there were 29 female, 7 male patients whose mean age was
55 41.5 ± 11.69 . According to the reason of discordance at the ablation outcome control, patient
56 group was divided into 2 groups: 15 (42%) patients (9 female, 6 male patients, mean age:
57 50.66 ± 10.73) who had metastatic lymph nodes as the reason of discordance constituted lymph
58 node group. Remaining 21 (58%) patients (19 female, 2 male patients, mean age: 41.5 ± 10.44)
59 were in micrometastatic group in which reason of discordance could not be determined.
60 There were statistically significant differences in soft tissue invasion ($p<0.003$), Tg levels
61 before RAI treatment ($p<0.002$), and diameter of tumor $>2\text{cm}$ ($p<0.035$) between patient and
62 control groups. Among patient group, male gender ($p<0.03$), diameter of tumor $>2\text{cm}$
63 ($p<0.05$), thyroid capsule invasion ($p<0.03$), and age >40 ($p<0.01$) were significantly different
64 between lymph node and micrometastatic group.

65 **Conclusion:** I-131 WBS/Tg level discordance at the ablation outcome control is mainly
66 caused by metastatic lymph nodes.

67 **Key Words:** Differentiated thyroid carcinoma, radioiodine ablation, I-131 whole body scan,
68 lymph node metastases.

69

70 INTRODUCTION

71 Differentiated thyroid cancers (DTC) constitute majority of all thyroid cancers (1).
72 Disease-free survival rate is more than 90% at 10 years (2), but still there is a group of
73 patients who suffer from persistent or recurrent disease.

74 Total or near-total thyroidectomy is the first step of the treatment. Then high dose
75 radioactive iodine-131 (I-131) (RAI) is given to the patient both to ablate the residual
76 thyroidal tissue and destroy the metastases. In routine practice, a low dose (1-2 mCi; 37-74
77 MBq) radioiodine scanning to assess the postoperative residual thyroid tissue and possible
78 metastatic foci is not done before RAI ablation because even with low doses of radioiodine,
79 stunning of the cells may occur which diminishes the uptake of RAI ablation dose. After RAI

80 ablation, thyroid stimulating hormone (TSH) suppression treatment with L-thyroxine is given
81 to the patient for the rest of his life to suppress the proliferative effect of TSH on thyroidal
82 tissues or metastases.

83 Ablation outcome is assessed (ablation outcome control) 6-12 months after high dose
84 RAI ablation. After the withdrawal of suppression treatment or administration of
85 recombinant TSH, TSH is expected to raise to minimum of 30 mIU/L. Stimulation of TSH
86 enables the augmentation of radioiodine uptake by the tissues. 1-5 mCi (37-185 MBq) of
87 radioiodine is given orally to the patient and after 48 hours, diagnostic I-131 whole body
88 scan (I-WBS) is done. During this process, levels of thyroglobulin (Tg) and anti-Tg antibodies
89 are also measured.

90 Tg is a thyroid-specific protein with diameter of 660 kDa which is the precursor
91 element of thyroid hormone biosynthesis (3). It is secreted from either normal thyroid tissue
92 or functioning metastases of thyroid cancer. It is predicted that after total/near-total
93 thyroidectomy and RAI ablation, Tg levels should be near zero. During the follow-ups, any
94 increased level of Tg suggests that there is a thyroid tissue which could not be ablated or
95 there are metastases. In the presence of anti-Tg antibodies, levels of Tg can be mistakenly
96 low.

97 Normally, there is a concordance between I-WBS and Tg levels. A negative I-WBS
98 and Tg level <2 ng/ml suggest that the thyroid tissue is totally ablated. On the other hand, a
99 positive I-WBS and $Tg \geq 2$ ng/ml point out residual disease and make the clinician continue
100 with further treatments. Whether continuing with further treatments or just monitoring the
101 patient closely with short time intervals are still debated because aggressive treatment of
102 minimal residual disease has not been proven to increase patient survival rates yet (4).

103 There are many investigations which revealed positive Tg level and negative I-WBS
104 discordance seen during follow-ups of patients, but there are only few articles about this
105 discordance which is detected at the ablation outcome control process. Therefore, in this
106 study, we compared features of patients whose I-WBS and Tg levels are negative in the

107 ablation outcome control with those of the patients with negative I-WBS, but positive Tg
108 levels. We investigated the cause of this discordance and the outcomes of the further
109 treatments.

110 **PATIENTS AND METHOD**

111 **Patients**

112 Thirty-six patients who had total or near total thyroidectomy and RAI ablation
113 because of differentiated thyroid cancer between 1992-2009 and whose I-WBS were negative
114 and Tg levels ≥ 2 ng/ml during ablation outcome control were taken as the patient group . For
115 the control group, 36 patients whose I-WBS were negative and Tg <2 ng/ml at the ablation
116 outcome control were selected randomly.

117 After TSH stimulation, 5 mCi (185 MBq) I-131 was given orally to the patients and 2
118 days later, I-WBS were done. The mean value for TSH was 108.8 mIU/L in patient group
119 and 93.7 mIU/L in control group. All Tg and anti-Tg antibody levels were obtained by
120 electrochemiluminescence method, simultaneously with TSH. During I-WBS scans, we took
121 whole body, anterior-posterior images. Also in every patient, static images of neck were
122 taken. We could not make SPECT or SPECT-CT imaging during radioiodine scanning.

123 In our study, ablation outcomes were assessed 6-15 months (mean: 10 months) after
124 RAI ablation.

125 The patients with high levels of anti-Tg antibodies or distant metastases had not been
126 selected for neither patient nor control groups. Therefore, none of the patients in our study
127 group had high levels of anti-Tg antibodies or distant metastases throughout their course of
128 follow-ups.

129 Low dose whole body radioiodine scanning before RAI ablation had not been done to
130 neither of the patients in order to prevent the stunning of the cells.

131 **Methods**

132 For the determination of factors which led to the discordance at the ablation outcome
133 control age, gender, histopathological features (such as diameter of tumor, subgroups,

134 multifocality, bilaterality, lymphatic invasion, vascular invasion, tumor capsule invasion,
135 thyroid capsule invasion, soft tissue invasion, intrathyroidal proliferation, rest tumor on
136 surgical margin), dose of ablation therapy, Tg measurements before ablation treatment, and
137 RAI uptake values during ablation were investigated statistically by using Ki-square, Mann-
138 Whitney U, and multivariate logistic regression analysis tests between patient and control
139 groups.

140 In patient group, the data which was gathered from the radiological or scintigraphical
141 studies that had been done to find out the reason of discordance was then evaluated. In most
142 of the patients, neck ultrasound (USG) was chosen. Computed tomography (CT) of thorax,
143 magnetic resonance (MR) of neck, and F18- fluorodeoxyglucose (FDG) positron emission
144 tomography (PET)-CT were chosen in less number of patients. According to this data, the
145 patient group was then divided into 2 groups, regarding the cause of the discordance.

146

147 **RESULTS**

148 In patient group, there were 28 female, 8 male patients whose mean age was
149 45.6 ± 11.39 . In control group, there were 29 female, 7 male patients, and the mean age was
150 41.5 ± 11.69 .

151 The histopathologic informations of the patients of both groups are given on Table 1.
152 In patient group, the information about size of tumor, multifocality, bilaterality, lymphatic
153 invasion, vascular invasion, tumor capsule invasion, thyroid capsule invasion, soft tissue
154 invasion, intrathyroidal proliferation, and rest tumor on surgical margin could not be found in
155 2 patients. In 1 of those patients, histopathologic subgroup was also unknown, although the
156 patient was introduced to our department as differentiated thyroid cancer patient.

157 The other features of the patients which were evaluated during statistical analysis are
158 given in Table 2. For any invasions of tumor or poor prognostic features, such as subtypes of
159 diffuse sclerosing, tall or columnar cell, age > 40 years old or diameter of tumor > 2 cm

160 ablation dose was chosen to be 150 mCi (5550 MBq) instead of 100mCi (3700 MBq). RAI
161 uptakes were measured at 24th hour.

162 6 patients in patient group and 10 patients in control group had cervical lymph node
163 dissections during their thyroidectomy operations. All of the dissected lymph nodes were
164 metastatic.

165 According to analysis between patient and control groups, there were statistically
166 significant differences in soft tissue invasion ($p<0.003$) and Tg values before ablation
167 ($p<0.002$). When patient and control groups were taken as dependent variables in multivariate
168 logistic regression analysis, soft tissue invasion ($p<0.004$, odds ratio (OR):12, % 95
169 confidence interval (CI): 2.19-66.77), Tg value before ablation ($p<0.001$, OR:1.07, 95%
170 CI:1.02-1.12), and tumor diameter >2 cm ($p<0.035$, OR: 5.45, 95% CI: 1.12-26.47) were
171 found to cause discordance.

172 After the ablation outcome control process, the causes of I-WBS and Tg level
173 discordance were evaluated in patient group. According to these data, patient group was
174 divided into 2 groups according to the cause of the discordance. The first group which was
175 named as lymph node group, consisted of 15 patients (42%) with lymph node metastases as
176 the cause of the discordance (9 female, 6 male patients, mean age: 50.66 ± 10.73). The lymph
177 nodes were 5.9-50 mm in diameter, measured either with USG or CT and were located mainly
178 on the neck, only few in mediastinum. Their mean diameter was 15.1 mm, median was 11
179 mm.

180 In the second group, there were 21 patients (58%): 19 female, 2 male patients, mean
181 age: 41.5 ± 10.44 . In this group, no particular cause could have been found. The reasons like
182 improper patient preparation or loss of iodine trapping were excluded either by questioning
183 the patients or by PET-CT scans in selected patients. Therefore for this group, we supposed
184 that the sizes of the metastases were too small to be able to be detected and therefore named
185 the group as micrometastatic group.

186 Between lymph node and micrometastatic groups, there were statistically significant
187 differences in male gender ($p<0.03$), tumor diameter >2 cm ($p<0.05$), thyroid capsule invasion
188 of the tumor ($p<0.03$), and age >40 years ($p<0.01$). When these groups were taken as
189 dependent variables in multivariate logistic regression analysis, only tumor diameter >2 cm
190 ($p<0.01$, OR:34.35, 95% CI: 1.79-655.76) and age >40 years ($p<0.008$, OR: 1.22, 95% CI:
191 1.05-1.42) remained significant.

192 Tumor diameter >2 cm increased the likelihood of both discordance in ablation
193 outcome control process and also the presence of lymph node metastases. Soft tissue invasion
194 of the tumor increased the likelihood of discordance. Tg level ≥ 10 ng/ml before ablation
195 increased the likelihood of discordance, whereas age >40 increased possibility of lymph node
196 metastases.

197 Follow-up range was 2-13 years (median: 3 years) in lymph node group and 2-24
198 years (median: 4 years) in micrometastatic group. The treatments which were given after the
199 detection of discordance to the patients are listed in Table 3.

200 In lymph node group, 11 patients received RAI treatment after the detection of cause
201 of discordance. There were radioiodine uptakes on the therapeutical whole body scans
202 (tWBS) which were done 10 days after RAI treatments in 9 patients (Fig.1). In one of the
203 patients who had surgery, a second primary tumor was detected.

204 In micrometastatic group, 11 patients received RAI treatments. In 6 patients, there
205 were radiiodine uptakes on tWBS (Fig.2).

206 As a summary, 24 of 36 patients received a treatment. Six of those were accepted as
207 in remission during the follow-ups, whereas in 7 patients, the treatment response had not been
208 controlled yet. In 11 patients, Tg levels were still high.

209 Eleven of 36 patients had not been given a treatment. After the follow-ups, 9 of those
210 patients were accepted either in remission or having a stable disease. In 2 patients, Tg levels
211 began to rise during controls. One of 36 patients got out of follow-up.

212 During follow-ups, no patient had any serious morbidity or mortality.

213 **DISCUSSION**

214 The patients who have DTC have quite a very long life span when compared with the
215 patients who have other types of malignancies. The overall 1-, 2-, 5-, and 10-year survival
216 rates are said to be 98.2%, 97.4%, 96.5%, and 96.5% respectively (5), but on the other hand,
217 the recurrence is common (15-30% of patients), even in early-stage disease (6). Early
218 diagnosis enables early treatment of residual disease when probably the treatment will be
219 more effective (4).

220 One of the problems that is frequently seen during the follow-ups of DTC patients is
221 Tg level and I-WBS discordance at the ablation outcome control which is a sign of residual or
222 metastatic disease. In our study, lymph node metastases were responsible of this discordance
223 in 42% of the cases. Also in our study, soft tissue invasion of the tumor, tumor diameter>2cm,
224 and Tg level ≥ 10 ng/ml before getting RAI ablation were found to cause discordance.
225 Similarly, Alzahrani et al found that perithyroidal tumor extension, soft tissue invasion,
226 cervical lymph node metastases and high Tg level before RAI ablation were associated with
227 discordance (7).

228 All histological variants of thyroid tumors are seen more frequently in females.
229 Papillary carcinoma has been found in 80% of female cases. Thyroid tumors usually occur in
230 the third, fourth, and fifth decades of life (8). As age gets older, the female/male ratio declines
231 from 5 at ages 20-24 to 3.4 at ages 35-44 and approaches to 1 at ages 80+ (9). In our study,
232 we found that in male gender and age>40, lymph node involvement which led to metastatic
233 disease was common. Zaydfudim et al revealed that lymph node involvement was associated
234 with 46% increased risk of death (10). Wada et al found that younger patients (≥ 45 years old),
235 even when they presented with palpable lymphadenopathy had a favorable prognosis (11).

236 The rate of neck lymph node metastases varies from 5-20 % (12) up to 70% (2) in
237 papillary thyroid cancers. In our study, male gender, tumor diameter >2cm, thyroid capsule
238 invasion, and age>40 were significantly associated with lymph node involvement. Very
239 similarly, Ito et al found that male gender, age 55 years or older, maximal tumor diameter

240 larger than 3 cm, and massive extrathyroid extension were associated with lymph node
241 involvement and they recommended prophylactic modified radical neck dissection (13).
242 Bardet et al emphasized that because almost half of lymph node metastases occurred in the
243 year following the diagnosis, it was probable that most patients with lymph node metastases
244 have persistent or residual disease rather than a recurrence (12). Similarly, in our patient
245 group, 11 patients had lymphatic invasion of the tumor and 6 patients had lymph node
246 metastases during the diagnosis and in 15 patients lymph node metastases were determined
247 during ablation outcome control process. High rate of lymph node detection during ablation
248 outcome control could have also been the result of the limited neck dissection which is
249 preferred in our hospital for the primary operation. During total thyroidectomy operations,
250 palpable, preoperatively detected lymph nodes which are also explored during the operation
251 are resected. The micrometastatic small lymph nodes which are not resected, grow in size
252 after a period of time. Limited neck dissection is associated with cervical recurrence (14).
253 Low et al found a significant inverse relationship between total number of lymph nodes
254 resected and Tg level at 12 month after the surgery (3).

255 When preoperative USG shows no malignant lymph nodes or shows only in the
256 central compartment, dissection of central compartment is sufficient, but if primary tumor is
257 large (≥ 4 cm) and/or there is distant metastasis, then there is high risk for recurrence in the
258 lateral cervical compartment (15). Also during reoperation, there is risk of having
259 complications. In a study, out of 22 neck reoperations, 2 patients developed permanent
260 hypoparathyroidism and 4 patients have permanent recurrent laryngeal nerve paralysis (16).
261 Gonzalez et al showed the effectiveness of preoperative USG in detecting nonpalpable
262 metastatic lymph nodes and recommended preoperative neck USG to optimize primary
263 surgical planning (17). Therefore, evaluating the patient before the operation and performing
264 the convenient neck dissection are essential. Both in preoperative state and also for the
265 discordant cases during the ablation outcome control as in our study, USG has a major role.
266 Especially, the patients who have discordance of Tg levels and I-WBS at the ablation

267 outcome control should have an USG, performed by an experienced radiologist because
268 normal anatomy of the neck is changed very much after neck surgeries. Small sizes of the
269 lymph nodes and postinflammatory lymph node hyperplasia are other reasons of insufficient
270 or wrong evaluation. (18). In the patients with high levels of Tg and negative I-WBS, the
271 detection of lymph nodes arises the chance for surgery. In our study, median size of the lymph
272 nodes in lymph node group was 11 mm which can be a reason for the negative I-WBS.
273 Because metastatic lymph nodes can be seen in 42% of the cases, in the patients with high
274 levels of Tg and negative I-WBS, USG done by an experienced radiologist must be the first
275 imaging modality to choose. Dedifferentiation of the tumor, iodine contamination , and low
276 dose of iodine are the other possible reasons for Tg positive/ I-WBS negative situation. For
277 our patient group, the main reason seems to be the small sizes of the lymph nodes. For this
278 reason, SPECT/CT may provide valuable information. Also focal radioiodine uptake in the
279 organs like salivary glands which concentrate iodine physiologically makes detecting
280 malignant deposits like lymph nodes harder (19). Again, SPECT/CT may provide valuable
281 information . In their investigation, Spanu et al showed that SPECT/CT had an incremental
282 value over planar images in 67.8% of patients, modified therapy in 35.6% of metastatic cases,
283 and avoided unnecessary treatment in 20.3% of patients because SPECT/CT identified
284 additional 28 occult foci than planar images in 10 of 52 patients, 14 occult foci in 7 patients
285 with negative planar images, and characterized 48 foci unclear on planar images in terms of
286 location and extent (20). In the investigation of Schmidt et al, SPECT/CT yielded a gain in
287 information on nodal staging in 35%, altered risk stratification in 25% when compared with
288 planar imaging (18). SPECT/CT has also a high negative predictive value in detecting
289 occurrence of cervical metastatic lymph nodes at the ablation outcome control (19).

290 Dedifferentiation is another reason for discordance. In 10-15% of DTC patients, high
291 levels of Tg are detected when radioiodine scans are negative (21). As a result of
292 dedifferentiation, tumors may lose their ability to trap radioiodine. In these patients,
293 instead of using radioiodine for whole body scanning, F18-FDG can be used for whole body

294 imaging in PET-CT cameras. As being a glucose analogue, F18-FDG is taken into the cells
295 by GLUT-1 transporters. In dedifferentiated tumors, there are increased numbers of GLUT-1
296 which enable the high uptake of F18-FDG (21,22). With its better resolution characteristics,
297 in patients with elevated Tg, but negative radioiodine scans, F18-FDG PET has sensitivity of
298 69.3-94.6%, specificity of 25-83%, and accuracy of 63.9-87.8% in detecting
299 recurrent/metastatic disease (23).

300 In our study, only 6 of the patients who had received a treatment after the detection of
301 discordance were in remission or accepted as having a stable disease. Eleven of the patients
302 that received a treatment had still high levels of Tg and accepted as having persistent disease.
303 On the other hand, in 9 patients who did not receive a treatment, Tg levels decreased. Only in
304 2 patients of no treatment group, Tg levels increased during the follow-ups. Alzahrani et al
305 reported similar outcomes: Of 53 patients, 42 cases were followed without any therapeutic
306 intervention. Thirty-one cases had spontaneous remission and 11 cases continued to have high
307 Tg levels. From the other 11 patients who had a therapeutic intervention (RAI, surgery, or
308 external radiotherapy), 4 cases achieved remission, 5 cases continued to have persistent
309 disease, and 2 cases had progression (7). Schmidt et al emphasized the efficacy of radioiodine
310 treatment in metastatic lymph nodes. In their investigation, 18 of 22 radioiodine positive
311 lymph nodes which are detected at the ablation were not detected at the ablation outcome
312 control on the average of 5 months (19). They also mentioned that lymph nodes smaller than
313 0.9 ml were eliminated by radioiodine 94%, whereas for the larger nodes, this rate was 1 out
314 of 4. For this reason, they stated that it was rational to use a threshold in this range for the
315 choice of radioiodine therapy or resurgery.

316

317 **CONCLUSION**

318 If there is a discordance of WBS (-), Tg (+) at the ablation outcome control, the first
319 thing which must be done is to search for metastatic lymph nodes. Only after the

320 determination of the cause of discordance with diagnostic studies, the choice of treatment
321 (radioiodine therapy or resurgery) can be evaluated.

322

323 **REFERENCES**

324 **1.** Silberstein EB. The treatment of thyroid malignant neoplasm. In: Henkin RE, Bova D,
325 Dillehay GL, Halama JR, Karesh SM, Wagner RH, Zimmer Am (ed). Nuclear Medicine.
326 Mosby Elsevier. Pennsylvania, USA, 2nd ed., 2006; pp 1576-1587

327 **2.** Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic
328 factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph
329 node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin
330 Endocrinol Metab. 2005; 90: 5723-29

331 **3.** Low H, Delbridge L, Sidhu S, Learoyd D, Robinson B, Roach P, et al. Lymph node status
332 influences follow-up thyroglobulin levels in papillary thyroid cancer. Ann Surg Oncol. 2008;
333 15: 2827-32

334 **4.** Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised
335 American Thyroid Association Management Guidelines for Patients with Thyroid Nodules
336 and Differentiated Thyroid Cancer. Thyroid. 2009; 19: 1-48

337 **5.** Lin YK, Sheng JM, Zhao WH, Wang WB, Yu XF, Teng LS, et al. Multifocal papillary
338 thyroid carcinoma: clinical analysis of 168 cases. Zhonghua Wai Ke Za Zhi. 2009; 47: 450-3

339 **6.** Johnson NA, Tublin ME. Postoperative surveillance of differentiated thyroid carcinoma:
340 rationale, technique, and controversies. Radiology. 2008; 249: 429-44

341 **7.** Alzahrani AS, Mohamed G, Al Shammary A, Aldasouqi S, Abdal- Salam S, Shoukri M.
342 Long-term course and predictive factors of elevated serum thyroglobulin and negative
343 diagnostic radioiodine whole body scan in differentiated thyroid cancer. J Endocrinol Invest.
344 2005; 28: 540-6

345 **8.** Manxhuka-Kerliu S, Devolli-Disha E, Gerxhaliu A, Ahmetaj H, Baruti A, Loxha S, et al.
346 Prognostic values of thyroid tumours. Bosn J Basic Med Sci. 2009; 9: 111-9

- 347 **9.** Kilfoy BA, Devesa SS, Ward MH, Zhang Y, Rosenberg PS, Holford TR, et al. Gender is an
348 age-specific effect modifier for papillary cancers of the thyroid gland. *Cancer Epidemiol*
349 *Biomarkers Prev.* 2009; 18:1092-100
- 350 **10.** Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement
351 on survival in patients with papillary and follicular thyroid carcinoma. *Surgery.* 2008; 144:
352 1070-7
- 353 **11.** Wada N, Masudo K, Nakayama H, Suganuma K, Matsuzu K, Hirakawa S, et al. Clinical
354 outcomes of older or younger patients with papillary thyroid carcinoma: impact of
355 lymphadenopathy and patient age. *J Canc Surg.* 2008; 34: 202-7
- 356 **12.** Bardet S, Malville E, Rame JP, Babin E, Samama G, De Raucourt D, et al. Macroscopic
357 lymph-node involvement and neck dissection predict lymph-node recurrence in papillary
358 thyroid carcinoma. *Eur J Endocrinol.* 2008; 158: 551-60
- 359 **13.** Ito Y, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, et al. Risk
360 factors for recurrence to the lymph node in papillary thyroid carcinoma patients without
361 preoperative detectable lateral node metastasis: validity of prophylactic modified radical neck
362 dissection. *World J Surg.* 2007; 31: 2085-91
- 363 **14.** Davidson HC, Park BJ, Johnson JT. Papillary thyroid cancer: controversies in the
364 management of neck metastases. *Laryngoscope.* 2008;118: 2161-5
- 365 **15.** Sugitani I, Fujimoto Y, Yamada K, Yamamoto N. Prospective outcomes of selective
366 lymph node dissection for papillary thyroid carcinoma based on preoperative ultrasonography.
367 *World J Surg.* 2008; 32: 2494-502
- 368 **16.** Mirghani H, Francois A, Landry G, Hans S, Menard M, Brasnu D. Repeat of lymphatic
369 dissection for thyroid cancers. *Ann Otolaryngol Chir Cervicofar.* 2009; 126: 37-42
- 370 **17.** Gonzalez HE, Cruz F, O'Brien A, Goni I, Leon A, Claire R, et al. Impact of preoperative
371 ultrasonographic staging of the neck in papillary thyroid carcinoma. *Arch Otolaryngol Head*
372 *Neck Surg.* 2007; 133: 1258-62

373 **18.** Schmidt D, Szikszai A, Linke R, Bautz W, Kuwert T. Impact of 131I SPECT/Spiral CT
374 on nodal staging of differentiated thyroid carcinoma at the first radioablation. J Nucl Med.
375 2009; 50: 18-23

376 **19.** Schmidt D, Linke R, Uder M, Kuwert T. Five months' follow-up of patients with and
377 without iodine-positive lymph node metastases of thyroid carcinoma as disclosed by I131-
378 SPECT/CT at the first radioablation. Eur J Nucl Med Mol Imaging. 2010; 37: 699-705

379 **20.** Spanu A, Solinas ME, Chessa F, Sanna D, Nuvoli S, Madeddu G. I131 SPECT/CT in the
380 follow-up of differentiated thyroid carcinoma: incremental value versus planar imaging. J
381 Nucl Med 2009; 50: 184-190

382 **21.** Shamma A, Degirmenci B, Mountz JM, McCook BM, Branstetter B, Bencherif BB, et al.
383 18F-FDG PET/CT in patients with suspected recurrent or metastatic well-differentiated throid
384 cancer. J Nucl Med 2007; 48: 221-226

385 **22.** Schlüter B, Bohuslavizki KH, Beyer W, Plotkin M, Buchert R, Clausen M. Impact of FDG
386 PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin
387 and negative I-131 scan. J Nucl Med 2001; 42: 71-76

388 **23.** Hussain HK, Britton KE, Grossman AB, Reznick RH. Thyroid cancer. In: Husband JE,
389 Reznick RH (ed). Imaging in Oncology. Taylor and Francis. London, UK, 2nd ed., 2004; pp
390 669-709

391

392

393

394

395

396

397

398

399

400 **Table 1:** Histopathologic features of the patients.

	Patient Group	Control Group
Diameter of tumor	>2 cm: 12 ≤2 cm: 22	>2cm: 6 ≤2 cm: 30
Histopathologic subgroup	Classical type papillary: 16 Nonclassical type papillary: 15 Follicular: 3 Other: 1	Classical type papillary: 15 Nonclassical type papillary: 19 Follicular: 0 Other: 2
Multifocality	(+): 5 (-): 29	(+): 14 (-): 22
Bilaterality	(+): 6 (-): 28	(+): 9 (-): 27
Tumor capsule invasion	(+): 12 (-): 22	(+): 16 (-): 20
Thyroid capsule invasion	(+): 25 (-): 9	(+): 16 (-): 20
Vascular invasion	(+): 11 (-): 23	(+): 5 (-): 31
Lymphatic invasion	(+): 11 (-): 23	(+): 10 (-): 26
Soft tissue invasion	(+): 18 (-): 16	(+): 7 (-): 29
Rest tumor on surgical margin	(+): 4 (-): 30	(+): 4 (-): 32
Intrathyroidal proliferation	(+): 13 (-): 21	(+): 12 (-): 24

401

402

403

404

405

406

407

408

409

410

411

412

413

Table 2: Clinical features of the patients.

	Patient Group	Control Group
Ablation doses *	100 mCi (3700 MBq): 13 150 mCi (5550 MBq): 23	100 mCi (3700 MBq): 14 150 mCi (5550 MBq): 22
Tg levels before ablation	<10 ng/ml: 4 ≥10 ng/ml: 23 Unknown: 9	<10 ng/ml: 23 ≥10 ng/ml: 10 Unknown: 3
RAI uptakes during ablation **	<5%: 9 ≥5%: 11 Unknown: 16	<5%: 14 ≥5%: 17 Unknown: 5

415

416

417

418

419

420

421

422

423

424

425

426

427

428

429

430

431

432

433

434

435

436

437

438

439

440

441

442

443

444

445

446

447

448

449

450

451
452

Table 3: Treatments given to the patients after the detection of discordance.

	Lymph node group (n:15)	Micrometastatic group (n:21)
Surgery	2	-
RAI	6	11
Surgery+RAI	5	-
No treatment	2	9
Unknown	-	1

453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473

474 **LEGENDS FOR ILLUSTRATIONS**

475 **Fig.1:** 41 years old, male patient. Although I-WBS was negative, Tg level was high
476 during ablation outcome control. Then he had an USG which revealed a lymph node at right
477 submandibular region. Although fine needle aspiration biopsy was benign, the patient was
478 given 150 mCi (5550 MBq). During RAI treatment his laboratory values were TSH: 93
479 mIU/L, Tg: 42.6 ng/ml, anti-Tg: 44 IU/ml (normal range: 0-115 IU/ml). An uptake is seen in
480 submandibular region which belongs to the lymph node.

481 **Fig.2:** 26 years old, female patient. I-WBS was negative, but Tg was high in her
482 ablation outcome control. There was neither a residual thyroid tissue, nor a metastatic focus
483 on the following diagnostics studies. She was given 150 mCi (5550 MBq) RAI treatment
484 when TSH: 64.64 mIU/L, Tg: 13.7 ng/ml, anti-Tg: 12.26 IU/ml (normal range: 0-115
485 IU/ml). An uptake is seen in mediastinum. In MR which was taken after tWBS, there was no
486 remnant of thymic tissue.

487