The Definition of Minimal Extrathyroid Extension in Thyroid Pathology by Analyzing Sizable Intra- and Extrathyroid Blood Vessels

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This certifies that the Master's Thesis of Hyae Min Jeon is approved.

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Hyae Min Jeon

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ABSTRACT

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Background: To define the exact boundary of the intra- and extrathyroid aspects of the gland when determining the extent of cancer invasion, we plan to clarify the definition of sizable vascular structures, one of the helpful histologic clues in determining minimal extrathyroid extension (ETE). We hypothesized that arterial wall thicknesses in extrathyroid soft tissue would be significantly different from arteries in the thyroid parenchyma.

Materials and methods: Twenty cases of papillary carcinoma were selected. The numbers and wall thicknesses of the arteries and arterioles in intra- and extrathyroid tissue were evaluated. The absence of nerve tissue in the thyroid gland was confirmed by the S-100 protein immunohistochemical stain.

Result: The comparison of the mean thicknesses (μm) of the total arteries between extrathyroid and intrathyroid tissues in the retrospective study (26.88 vs. 15.07) and the prospective study(35.24 vs. 16.52) revealed significant differences (p=0.000). The greatest thickness of intrathyroidal arteries was 67.93 μm.

Conclusion: With a result, the study showed that the extrathyroidal arteries were significantly thicker than intrathyroidal arteries. We suggest that the sizable blood vessel of extrathyroidal arteries should be greater than 67.93 μm in thickness.

Key words : Sizable blood vessels, Minimal extrathyroidal extension, Thyroid, Papillary carcinoma, T Staging

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I. INTRODUCTION

There has been much progress in diagnosing and reporting thyroid carcinomas. However, many uncertainties and controversies still remain. Among them, the definition of minimal extrathyroid extension (ETE), which is known as one of the prognostic factors of thyroid carcinoma, must be clarified [1]. Embryologically, anatomically, or histologically, there is no evidence that the thyroid gland has a complete or continuous fibrous capsule in living patients [2,3] or autopsy cases [4]. This is why it is difficult to define the exact boundary of extra- and intrathyroid tissues when determining the extent of cancer invasion. Several histological criteria have been presented for determining cancer extension to extrathyroid tissue, including perithyroid soft tissue, adipose tissue, skeletal muscle, sizable vascular structures, and nerves [5]. Some of these components can be helpful. For example, adipose tissue can be identified in the thyroid parenchyma under normal conditions [2] or may be related to carcinomas [6]. In addition, skeletal muscle can be the hallmark of ETE in the lateral lobes of the thyroid gland. However, it is problematic in the isthmus [5]. In fact, none of these histological criteria fall under the discrete criteria of ETE.

One of the major parameters for determining primary tumor stage (T) 2 and 3 depends on whether the cancers extend to the extrathyroid tissue or are limited to the thyroid parenchyma [7-10]. As a result, the anatomic stage of the tumor is evaluated. Therefore, it is important to precisely report the cancer extent even though it is difficult and problematic to accurately interpret the histology of the anatomic findings of the thyroid gland. Several previous studies stated some variable opinions about patient outcome according to the histological extent of thyroid gland cancer [11-14].

In this article, we focused on the exact definition of "sizable blood vessels" as mentioned above . The thyroid gland is nourished by arteries from the inferior thyroid artery, which is derived from the subclavian artery, and the superior thyroid artery, from the external carotid artery [2]. These arteries anastomose on or in the thyroid parenchyma. In practice, pathologists observe many vascular structures in the thyroid parenchyma and perithyroid soft tissue when diagnosing surgical specimens of total or partial thyroidectomies for cancer treatment. Determining the extent of carcinoma is confusing based on the blood vessels including what and how to measure the vessels or what to use the cut-off value. For practical purposes and academic interests, we plan to clarify and create a realistic definition of sizable blood vessels.

As stated above, the aim of our study was to suggest a numeric standard of sizable vascular structures as a parameter of minimal ETE of papillary carcinomas. We hypothesized that the mean thicknesses of blood vessel walls (arteries and arterioles only) exhibited a significant difference between extra- and intrathyroid tissues. The additional aim in this study was to confirm the absence of nerve tissue in thyroid parenchyma [2].

II. MATERIALS AND METHODS

1. Patient selection

Patients diagnosed with papillary carcinoma or microcarcinoma and who underwent surgery at Severance Hospital from January to June 2011 were included in this study. First, a preliminary study was performed in a retrospective manner. Ten cases of total thyroidectomy specimens with papillary carcinoma or microcarcinoma were randomly selected in age- (3rd to 7th decades) and sex-matched pairs. A representative hematoxylin-eosin (H&E) slide for each of the ten cases was analyzed. Prospectively, ten patients were randomly selected. All patients had neither medical history of hypertension or diabetes, nor surgical history of vascular diseases. The study design and case selection were identical to the retrospective study, but the entire unilateral thyroid gland containing the papillary carcinoma or microcarcinoma was serially dissected, sampled, and evaluated for each patient. We defined the location of vessels as either extrathyroid or intrathyroid by drawing imaginary lines in uncertain areas. Afterward, we counted and analyzed the arteries and arterioles.

2. Special and immunohistochemical staining

Thyroid tissue sections 3 μm in thickness, fixed in 10% formalin and embedded in paraffin blocks, were used for histological analysis with routine H&E stain and special and immunohistochemical stains of Elastic Van Gieson (EVG) and S-100 protein. Through the H&E stain, we could screen sections of thyroid tissue. To identify the types of vessels as either arteries or veins, the number of arteries was counted, and the arterial wall thickness between the intimal lining and external elastic lamina was precisely measured and eventually corrected for errors of sectioning and analyzing. We performed the special staining of EVG [15], and an additional immunohistochemical staining of S-100 proteins was completed to confirm the absence of nerve tissue in the thyroid parenchyma, as in previous studies [2].

3. Arterial/arteriolar wall thickness

Comparing extrathyroid and intrathyroid arterial/arteriolar wall thicknesses, we initially counted and measured the entire detectable artery. However, several large arteries in the thyroid gland could be a part of the branching arteries penetrating the thyroid along the interlobular spaces [2]. In addition, diagnostic problems, whether the cancer extended to the extrathyroid tissue or confined to the intrathyroid region, occurred when the cancer locations were not definitive. As a result, definite arteries/arterioles located in the intrathyroid and interlobular areas were excluded. Therefore, we decided not to include arteries or arterioles in the thyroid parenchyma that were greater than 2 mm from the surface.

We measured the arterial or arteriolar wall thicknesses, the distance between the intimal endothelium and external elastic lamina, which refers to the sum of the tunica intima and tunica media [15] using the image J program, one of the computer-based morphometric analysis programs [16] (Fig. 1). To avoid bias, we randomly measured the thicknesses six times, for example, at 12, 2, 4, 6, 8, and 10 o'clock, in each blood vessel [17,18] and used the mean thicknesses as statistical data, as shown in Fig. 2.

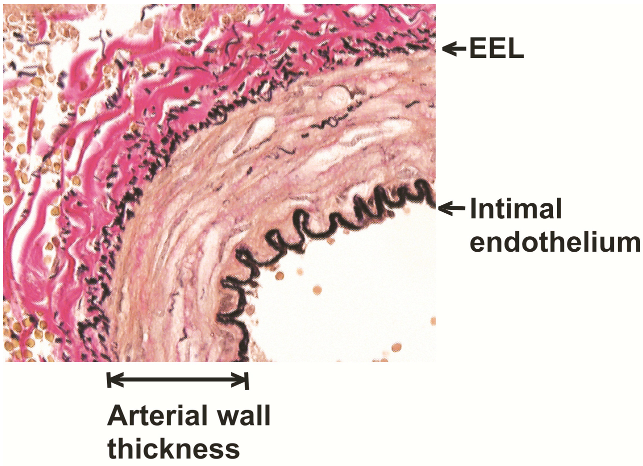

Fig. 1. Measurement of arterial wall thickness. We defined the thickness as the distance between the intimal endothelium and external elastic lamina (EEL), which refers to the sum of the tunica intima and tunica media. (Elastic Van Gieson stain, x200)

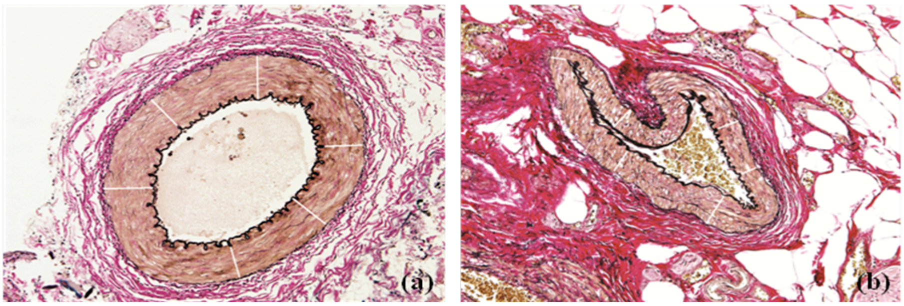

Fig. 2. Examples of six random measurements in the representative photomicrographs of extrathyroid arteries, expressed as white straight lines, showing relatively even (a) and irregular (b) wall thicknesses. When the arteries exhibited alternative irregular wall thickness, as shown in (b), we alternated six random measurements between the thin and thick parts of the wall. (Elastic Van Gieson stain, x100)

4. Statistical analysis

Data was analyzed using IBM SPSS for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). A two-tailed independent Student's t-test and Pearson's simple correlation coefficient were used for continuous variables of two independent groups in both studies. Statistical significance was inferred when $p < 0.05$.

III. RESULTS

A total 297 and 19,843 arteries were counted in ten retrospective and ten prospective patients, respectively. In the retrospective study, the extrathyroid arteries and arterioles (n=164) outnumbered the intrathyroid ones (n=133). In the prospective study, the extrathyroid arteries or arterioles (n=6,020) were fewer in number than the intrathyroid ones (n=13,823). The mean wall thicknesses (μm) of the extrathyroid arteries or arterioles (26.88 and 35.24) were thicker than the intrathyroid ones (15.07 and 16.52) in both the retrospective and prospective studies, resepctively (p=0.000). The respective ranges of mean thicknesses of the blood vessels in the extrathyroid and intrathyroid tissues were 3.84 to 226.43 and 3.25 to 67.93 in 20 total patients, respectively (Table 1).

Table 1. Comparison of arterial wall thickness in all cases according to the location

	Retrospective cases (n=297)		Prospective cases (n=19843)	
Parameters	Extrathyroid	Intrathyroid	Extrathyroid	Intrathyroid
Number (n)	164	133	6,020	13,823
Mean (μm) ± SD	26.88 ±23.79[1]	15.07±9.28	35.24±26.40[2]	16.52±7.78
Range of thickness (μm)	6.14-137.48	4.67-58.41	3.84-226.43	3.25-67.93

[1,2]P=0.000, between extrathyroid and intrathyroid

Wall thickness comparison between sexes according to the location of arteries is shown in Table 2. Counting numbers of the observed total arteries and arterioles demonstrated that male patients (n=11,535) had more arteries than female patients (n=8,605). This discrepancy was also seen in the number of extrathyroid (M vs. F= 3,217 vs. 2,967) and intrathyroid (M vs. F= 8,318 vs. 5,638) arteries for all the cases. In male patients, the mean extrathyroid arterial walls (23.47 and 32.11) were thicker than the intrathyroid arterial walls (14.33 and 14.22) in the preliminary (p=0.001) and prospective studies (p=0.000). Likewise, the female patients revealed the same results, with the mean extrathyroid arterial walls (29.83 and 38.66) being thicker than the intrathyroid arterial walls (15.78 and 19.93) in the preliminary (p=0.000) and prospective studies (p=0.000).

Table 2. Comparison of arterial wall thicknesses in male and female patients according to the location in two studies

Group of cases	Sex	Location	Range of thickness (μm)	Mean (μm) ± SD	P-value
Retrospective cases (n=297)	M (n=141)	Extrathyroid (n=76)	6.78-137.48	23.47±21.01	0 .001
		Intrathyroid (n=65)	4.67-58.41	14.33±9.31	
	F (n=156)	Extrathyroid (n=88)	6.14-115.47	29.83±25.72	0 .000
		Intrathyroid (n=68)	6.42-54.09	15.78±9.27	
Prospective cases (n=19,843)	M (n=11,394)	Extrathyroid (n=3,141)	3.84-226.43	32.11±26.59	0 .000
		Intrathyroid (n=8,253)	3.25-42.81	14.22±6.06	
	F (n=8,449)	Extrathyroid (n=2,879)	6.12-185.19	38.66±25.77	0 .000
		Intrathyroid (n=5,570)	4.36-67.93	19.93±8.73	

Table 3 showed that there was no significant difference in mean extrathyroid (p=0.083) or intrathyroid (p=1.000) arterial wall thicknesses between male and female patients in the preliminary study. However, in the prospective study, a comparison between paired mean extrathyroid (p=0.000) and intrathyroid (p=0.000) arterial wall thicknesses demonstrated that male arteries (32.11 and 14.22) were thinner than female arteries (38.66 and 19.93, respectively.

Table 3. The differences of arterial wall thicknesses between extrathyroid and intrathyroid tissues according to sex in two studies

Group of cases	Location	Sex	Range of thickness (µm)	Mean (µm) ± SD	P-value
Retrospective cases	Extrathyroid (n=164)	M (n=76)	6.78-137.48	23.47±21.01	0.083
		F (n=88)	6.14-115.47	29.83±25.72	
	Intrathyroid (n=133)	M (n=65)	5.35-58.41	14.33±9.31	1.000
		F (n=68)	6.42-54.09	15.78±9.27	
Prospective cases	Extrathyroid (n=6,020)	M (n=3,141)	3.84-226.43	32.11±26.59	0.000
		F (n=2,879)	6.12-181.32	38.66±25.77	
	Intrathyroid (n=14,039)	M (n=8,253)	3.25-42.81	14.22±6.06	0.000
		F (n=5,570)	4.36-67.93	19.93±8.73	

We identified the correlations between arterial wall thicknesses and age groups in the prospective cases (Table 4). All five age groups (3rd to 7th decades) revealed that the mean arterial wall thicknesses in extrathyroid tissue was thicker than the mean arterial wall thicknesses in intrathyroid tissue (p=0.000). In each age group, the mean wall thicknesses of arteries in extrathyroid and intrathyroid tissues exhibited significant differences (p=0.000) in ascending order (from 3rd to 7th decades) as follows: 36.15 vs. 18.71, 34.30 vs. 17.99, 32.68 vs. 17.20, 34.59 vs. 14.89, and 37.44 vs. 15.25, respectively. The preliminary study was excluded due to the limitation of cases.

Table 4. Relations of extrathyroidal and intrathyroidal arterial wall thicknesses among five age groups in the prospective cases

Age group	Location	Range of thickness (μm)	Mean (μm) ± SD	P-value
3rd decade (n=2,797)	Extrathyroid (n=1,032)	4.94-210.30	36.15±26.52	0.000
	Intrathyroid (n=1,765)	3.87-50.94	18.71±8.38	
4th decade (n=4,192)	Extrathyroid (n=1,116)	6.80-226.43	34.30±25.70	0.000
	Intrathyroid (n=3,076)	3.93-67.93	17.99±9.78	
5th decade (n=3,137)	Extrathyroid (n=911)	3.84-209.06	32.68±27.90	0.000
	Intrathyroid (n=2,226)	3.25-58.86	17.20±7.93	
6th decade (n=4,903)	Extrathyroid (n=1,424)	6.15-189.21	34.59±24.96	0.000
	Intrathyroid (n=3,479)	4.80-44.73	14.89±5.56	
7th decade (n=4,814)	Extrathyroid (n=1,537)	6.48-219.95	37.44±27.04	0.000
	Intrathyroid (n=3,277)	4.36-41.71	15.25±6.53	

When comparing among age groups, a decreasing tendency in the intrathyroid arterial wall thickness with increasing age was seen (p=0.01). On the other hand, the extrathyroid arterial wall thicknesses did not exhibit any significant relationship to age (p=0.09).

In addition, nerve tissues were not identified in the thyroid parenchyma itself but some in the interlobular septum of all cases by using immunohistochemical staining of the S-100 protein (Fig. 3).

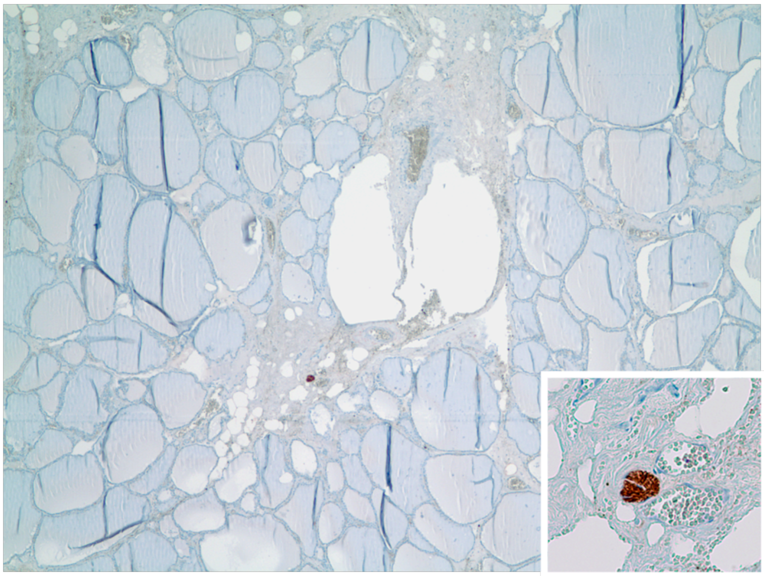

Fig. 3. Some nerve tissues were identified in the interlobular septum, but not revealed in the thyroid parenchyma itself, as reported in previous studies. (S-100 protein, x40, inset x200)

IV. DISCUSSION

Through the practice of surgical pathology, we found many difficulties determining the extent of tumors for diagnosing papillary carcinomas or papillary microcarcinomas of the thyroid gland. According to the primary tumor stage (T), the T3 stage classification was determined when the tumor size was greater than 4 cm in its greatest dimension, limited to the thyroid parenchyma, or any cancer with minimal ETE. Even though the anatomic stage/prognostic groups for papillary carcinomas in patients younger than 45 years had only two stages (I, II) whether metastasis was present or not, the T stage could be an important parameter for determining prognostic groups in patients 45 years and older [7-10]. Because of this significance, pathologists should discreetly judge whether tumors are limited to the thyroid. Searching previous articles and textbooks, however, we could not find discrete clarifying parameters of minimal ETE. Therefore, we focused on the aspect of "sizable blood vessels" in determining minimal ETE [5].

In this study, we found that the mean extrathyroid arteries were thicker than the intrathyroid arteries in both retrospective and prospective studies. Including all cases, extrathyroid arteries are 1.78 and 2.13 times thicker than intrathyroid arteries in retrospective and prospective studies, respectively. The thinnest extrathyroid artery was 3.84 μm in thickness, while the thickest intrathyroid artery was 67.93 μm in thickness. In the male group, the extrathyroid arteries were 1.64 and 2.26 times thicker than the intrathyroid arteries. In the female group, the differences were 1.89 and 1.94 times in thickness for the retrospective and prospective studies, respectively. In other words, the arteries in extrathyroid tissue were about two times thicker than arteries in thyroid parenchyma.

The total numbers of arteries were counted in each study. The retrospective study revealed that extrathyroid arteries (n=164) were greater in number than intrathyroid arteries (n=133), but the prospective study revealed the opposite result (6,020 vs. 13,823) for extrathyroid and intrathyroid arteries, respectively. One potential reason for this was that the each representative slide in the ten prospective cases included papillary carcinomas or papillary microcarcinomas. As a result, the area of thyroid parenchyma that could be examined decreased. Comparing the number of arteries between sexes, we found that the male group had more arteries than the female group.

We also found that the extrathyroid and intrathyroid arteries exhibited no sexual differences in the retrospective study. However, the prospective study revealed that the female arteries were 1.20 and 1.40 times thicker than male arteries in extrathyroid and intrathyroid tissues, respectively.

With regard to age difference, a correlation was not identified in the retrospective study due to the limited case number. In the prospective study, the total number of arteries revealed that the 6th decade group had the most arteries (n=4,903), while the 3rd decade group exhibited the fewest number of arteries (n=2,797). The relationships among age groups in the 3rd, 4th, 5th, 6th, and 7th decades were analyzed in the prospective study as follows: 1) all five age groups revealed that the arteries in extrathyroid tissue were thicker than in intrathyroid tissue, 2) in each decade, the results of the differences of arterial wall thicknesses between the location of arteries increased in ascending order of age with the extrathyroid arteries being 1.93, 1.90, 1.90, 2.32, and 2.43 times thicker than intrathyroid arteries. For all cases, a two-fold difference in thickness of extrathyroid and intrathyroid arterial walls was seen.

In addition, we confirmed that nerve tissue did not exist in the thyroid parenchyma, in agreement with previous studies [3].

Previous studies only mentioned the "sizable blood vessels" as one of the factors determining the boundary between intra- and extrathyroid tissues, whereas our study presented the "sizable blood vessels" numerically. However, the numbers of patients were insufficient to establish numeric criteria of sizable blood vessels. We included only arteries and arterioles as vessels in order to remove measurement error. We also calculated the mean thicknesses of the arteries and arterioles by randomly measuring each artery and arteriole a total of six times, as in previous studies [17,18]. Further larger studies are required in order to establish new criteria for sizable blood vessels and should include more precise measurement methods. With the publication of investigations about the prognostic differences according to minimal ETE, the demand for realistic criteria of sizable blood vessels will increase.

V. CONCLUSION

In conclusion, the retrospective study exhibited differences between extra- and intrathyroid arterial and arteriolar wall thicknesses regardless of sex. The later prospective study revealed that extrathyroid arteries were thicker than intrathyroid arteries in all 20 cases regardless of sex or age group.

The ranges of mean thicknesses (μm) of the blood vessels in the extrathyroid and intrathyroid tissues were 3.84 to 226.43 and 3.25 to 67.93 in 20 total patients, respectively. Therefore, we suggest that the sizable blood vessel of extrathyroid arteries should be greater than 67.93 μm in thickness.

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ABSTRACT(IN KOREAN)

갑상샘 암 진단에서 측정 가능한 갑상샘 실질 내, 외의 혈관 분석을 통한 갑상샘 암의 최소 갑상샘 외 침윤의 정의

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전혜민

배경: 갑상샘 암의 실질 외의 최소 침습 여부를 판단할 때 도움을 받을 수 있는 조직학적 단서들이 있다. 본 연구에서는 그 중 하나인 측정 가능한 혈관을 명확히 수치화하고자 하였고, 갑상샘 실질 외 연부 조직의 동맥 혈관벽 두께를 측정했을 때 실질 내 혈관보다 유의미하게 두꺼울 것이라는 가설을 설정하였다.

재료 및 방법: 갑상샘 암으로 진단받고 수술 받은, 임의로 추출한 스무 개의 증례를 나이 및 성별로 묶어서 실질 내, 외의 동맥 및 세동맥의 혈관 숫자 및 두께를 측정하였다. 또한, S-100 단백 면역화학 조직염색을 통하여 갑상샘 실질 내에 신경 조직이 존재하지 않음을 추가로 규명하고자 하였다.

결과: 갑상샘 실질 내, 외의 전체 동맥 및 세동맥 혈관 벽의 평균 두께를 비교한 결과, 후향적 연구 열 례 (15.07 μm 대 26.88 μm) 및 전향적 연구 열 례 (16.52 μm 대 35.24 μm) 모두에서 통계적으로 유의하게 실질 외의 혈관 벽이 더 두꺼웠다 (p=0.000). 가장 두꺼운 갑상샘 실질 내 동맥 혈관벽의 두께는 67.93 μm 였다.

결론: 따라서, 본 연구에서는 갑상샘 암의 T병기에 중요한 영향을 미치는 최소 침습 여부를 진단하는데 있어, 측정 가능한 혈관에 대한 정의를 제안하고자 하였고, 명백한 경우가 아닌 판단이 어려운 경우, 동맥 혈관벽의 두께를 측정했을 때 최소한 67.93 μm 보다 두꺼울 경우에는 갑상샘 외의 혈관으로 간주할 수 있음을 제안하고자 한다.

핵심되는 말 : 측정 가능한 혈관, 최소 갑상샘 외 침윤, 갑상샘, 유두암, T병기