Auris Nasus Larynx xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Auris Nasus Larynx

journal homepage: www.elsevier.com/locate/anl

Thick tumor capsule is a valuable risk factor for distant metastasis in follicular thyroid carcinoma☆

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ARTICLE INFO

Article history:
Received 19 January 2017
Accepted 1 May 2017
Available online xxx

Keywords:
Follicular thyroid carcinoma
Distant metastasis
Risk factor
Tumor capsule
Thick capsule

ABSTRACT

Objective: While the biological behavior of follicular thyroid carcinoma (FTC) has been studied in great detail using clinical experience, few studies have investigated pre- or intraoperative factors related to the risk of distant metastasis (DM) among patients with FTC. The aim of this study was to analyze the characteristics of FTC with DM.

Methods: This study retrospectively investigated 102 patients with FTC who underwent surgery between 1988 and 2013. We compared clinicopathological characteristics between FTC with and without DM.

Results: Univariate analysis revealed nodal metastasis ($p = 0.045$), serum thyroglobulin (Tg) at initial operation (≥1000 ng/ml; $p < 0.0001$), widely invasive appearance according to macroscopic findings ($p < 0.0001$), thick tumor capsule (≥1 mm; $p < 0.0001$), vascular invasion ($p = 0.0003$), extrathyroidal invasion ($p = 0.047$), and venous tumor embolism ($p = 0.045$) as significant risk factors for DM. Multivariate analysis conducted using pre- and intraoperative factors identified thick tumor capsule (≥1 mm), serum Tg at initial operation (≥1000 ng/ml), and macroscopically widely invasive appearance as risk factors independently associated with development of DM.

Conclusion: Patients with these risk factors should undergo total thyroidectomy and radioactive iodine ablation.

1. Introduction

Follicular thyroid carcinoma (FTC) is defined according to capsular invasion, vascular invasion, and metastasis. Because FTC cannot theoretically be diagnosed via fine-needle aspiration biopsy, distinguishing FTC from follicular adenoma is difficult [1]. Considerable inter-observer variability is also seen in the histopathological diagnosis of FTC. FTC metastasizes to distant organs, such as the lung and bone, rather than to the lymph nodes, and outcomes are worse than those of papillary thyroid carcinomas (PTC). By contrast, FTC without distant metastasis (DM) is a non aggressive disease with good prognosis.

Total thyroidectomy followed by radioiodine therapy is widely accepted as a useful mode of treatment for FTC with DM, but the optimal treatment for FTC without DM remains controversial. The ability to predict which cases of FTC would develop DM would assist with treatment planning. While the biological behavior of FTC has been studied in great detail

☆ Presented at the 13th Asian Association of Endocrine Surgeons Congress on April 26–28, 2012 in Singapore.

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http://dx.doi.org/10.1016/j.anl.2017.05.002
0385-8146/

using clinical experience, few studies have investigated pre- or intraoperative factors related to the risk of DM among patients with FTC. The purpose of this study was to identify initial clinical and histopathological features of FTC that are risk factors for DM.

2. Materials and methods

2.1. Patient population

Cancer Institute Hospital is a tertiary oncology referral center in Tokyo, Japan. Between January 1988 and December 2013, a total of 120 patients with FTC underwent initial surgery at our institute. We excluded eight patients from this study due to a lack of data regarding thyroglobulin (Tg) levels at the time of the initial operation, and also 10 patients who had concomitant FTC and PTC. We included cases of FTC with poorly differentiated components (PC) showing insular, trabecular, or solid patterns of growth, although these cases are defined as having poorly differentiated carcinoma according to the 2004 World Health Organization classification. Preoperatively, all patients underwent ultrasonography (US) by the same radiologist (K.Y.) to assess tumor size, thickness of the tumor capsule, and the presence of intrathyroidal spread of FTC, extrathyroidal invasion (EX), and lymph node metastases. Chest computed tomography (CT) was routinely used to assess lung and mediastinal metastases. Contrast-enhanced CT of the neck was carried out to identify EX and lymph node metastases, if needed. Total thyroidectomy was performed when a tumor showed DM or factors associated with a high risk of developing DM, such as a widely invasive appearance. When a tumor was limited to one lobe without DM and was indistinguishable from follicular adenoma, hemithyroidectomy of the affected side was performed with nodal dissection of the central zone. All patients were continuously followed as outpatients via physical examination, measurement of serum Tg, neck ultrasonography, chest X-ray, and, when necessary, CT, scintigraphy, and magnetic resonance imaging to detect recurrences in the remnant thyroid and/or distant organs after initial surgery.

2.2. Classification of groups

We classified patients with FTC into a DM-positive group (Group DM+; n = 38) and a DM-negative group (Group DM−; n = 64). Group DM+ included patients who presented with DM at the time of initial operation (Group DM1; n = 28) or who developed DM during follow-up (Group DM2; n = 10). Group DM− comprised patients who did not develop DM at any time during follow-up.

Medical records were retrospectively reviewed in relation to clinicopathological factors including age, sex, tumor size, lymph node metastasis, serum concentration of Tg at initial operation, macroscopic invasive appearance, thickness of the tumor capsule, vascular invasion, PC, EX, and venous tumor embolism. When US or intraoperative macroscopic examinations identified a lack of continuity in the tumor capsule, the tumor was regarded as having a widely invasive appearance (Fig. 1). We assessed capsular thickness by US or perioperative macroscopic examinations. The whole tumor capsule is not always homogenous. We measured the thickness of the thinnest part of the tumor capsule, and patients with a tumor capsule ≥1 mm thick were classified as having a thick tumor capsule (Fig. 2). If FTC shows a predominant PC (≥80% of tumor area), diagnosis may be made from intraoperative pathological examination. We therefore used the presence of a PC comprising ≥80% of the examined tumor as a preoperative or intraoperative risk factor for DM among patients with FTC. The degree of EX was classified as EX0, 1, or 2 in accordance with the criteria of the Japanese Society of Thyroid Cancer. Tumor with only minimal invasion, such as invasion to the sternothyroid muscles or perithyroid soft tissue, was classified as EX1. Tumor with massive invasion, such as invasion to subcutaneous soft tissues or to the larynx, trachea, esophagus, and recurrent laryngeal nerve, was classified as EX2. As the aim of this study was to predict which patients with FTC are liable to develop DM, we focused on risk factors that could be evaluated pre- or intraoperatively. To determine prognostic factors in patients with DM, uni- and multivariate analyses were conducted.

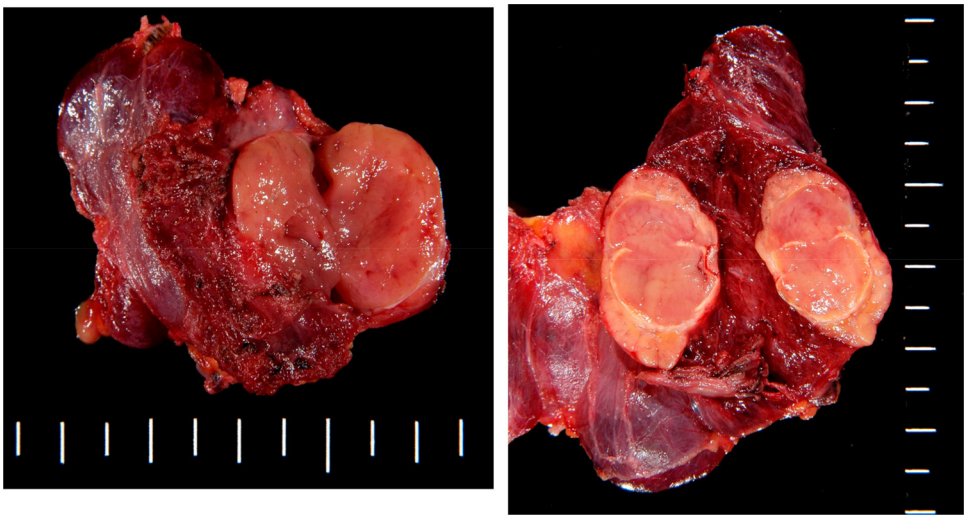

Fig. 1. Macroscopic findings for the two types of capsular invasion. (A) Minimally invasive appearance. (B) Widely invasive appearance.

Please cite this article in press as: Shimbashi W, et al. Thick tumor capsule is a valuable risk factor for distant metastasis in follicular thyroid carcinoma. Auris Nasus Larynx (2017), http://dx.doi.org/10.1016/j.anl.2017.05.002