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Clinical outcome of different modes of resection in papillary thyroid carcinomas with laryngotracheal invasion

Nobuyuki Wada · Hirotaka Nakayama · Yoshihiko Masudo · Nobuyasu Suganuma · Yasushi Rino

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Abstract
Aim The aim of this study is to evaluate the outcome of different modes of resection in papillary thyroid carcinoma (PTC) with laryngotracheal invasion.
Materials and methods Sixty-four primary PTCs with laryngotracheal invasion between 1964 and 2003 were retrospectively analyzed (17 men and 47 women; mean age, 61.6 years; mean follow-up, 92.3 months). Thirteen curative resections included six pharyngolaryngoesophagectomies, two total laryngectomies, and five circumferential resections (complete surgery). Eighteen patients who were candidates for curative resection refused to undergo complete surgery to avoid functional impairment, especially laryngeal function (incomplete surgery). Thirty-three patients with minimal invasion underwent shave or partial resection (conservative surgery). Clinical outcomes were compared between the three groups. The influence of different types of surgery and invasion was also evaluated by Cox proportional hazard analysis.
Results Three (23.1%) complete, 17 (94.4%) incomplete, and 4 (13.8%) conservative surgery patients died of disease ($P<0.0001$). The 10-year disease-specific survival (Kaplan–Meier) in complete, incomplete, and conservative surgery patients were 62.9, 11.1, and 87.7%, respectively (log rank test, $P<0.0001$). Incomplete surgery related to worse prognosis [$p<0.0001$; hazard ratio (HR), 12.9) than complete or conservative surgery. Tracheal deep invasion ($p=0.0019$, HR 7.6) and larynx invasion ($p<0.0001$, HR 9.9) related to worse prognosis than minimal invasion.
Conclusion Curative resection improves clinical outcomes in PTCs with laryngotracheal invasion. Conservative resection for minimal invasion also can achieve favorable prognosis. The degree of tumor invasion is significantly related to survival.

Keywords Complete surgery · Incomplete surgery · Shave resection · Laryngotracheal invasion · Papillary thyroid carcinoma

N. Wada (✉) · H. Nakayama · N. Suganuma · Y. Rino
Department of General Surgery, Yokohama City University,
3-9 Fukuura, Kanazawa-ku Yokohama,
Kanagawa 236-0004, Japan
e-mail: Wadan523@aol.com

N. Wada · Y. Masudo
Department of General Surgery,
Yokohama City University Medical Center,
4-57 Urafune-cho, Minami-ku Yokohama,
Kanagawa 232-0024, Japan

Introduction

Papillary thyroid carcinoma (PTC) with laryngotracheal invasion often has an adverse prognosis. Whether curative resection for such locally advanced PTCs improves clinical outcome remains a matter of debate. Extended radical resection increases the risks of serious complications or functional impairment of the neck. Expected benefits must therefore be carefully considered against potential risk in candidates for complete surgery.

Many authors [1–9] have recommended curative resection as the treatment of choice for thyroid carcinomas, whereas others [10–16] have reported that comparable results can be obtained by conservative resection with or without adjuvant therapies. Previous investigations assessing the outcomes of surgery for invasive thyroid carcinomas have included many histological types such as papillary, follicular, Hürthle cell, medullary, and anaplastic carcinomas. Moreover, some studies have included bulky

tumors considered clearly unresectable. The present analysis excluded such cases.

In this study, we focused on the treatment of PTC with laryngotracheal invasion. All 64 of our patients had primary PTC invading the larynx, trachea, or both and were considered candidates for curative resection on the basis of preoperative radiological examinations and intraoperative findings. However, 18 patients did not consent to complete surgery because of the risk of compromising neck (primarily laryngeal) function. Additionally, 33 patients underwent conservative surgery (shave or partial resection) because of minimal invasion.

We retrospectively evaluated clinical outcome by mode of resection, i.e., complete, incomplete, or conservative surgery, in PTCs with laryngotracheal invasion.

Materials and methods

From January 1964 through December 2003, 64 primary PTCs presenting with laryngotracheal invasion were initially operated on at Yokohama City University Hospital and Medical Center. All resected tumors were pathologically confirmed to be papillary carcinoma of the thyroid. Clinicopathological data from the 64 patients were retrospectively evaluated. There were 17 men and 47 women. The age at initial treatment ranged from 36 to 85 years (mean, 61.6 years). The mean duration of follow-up was 92.3 months with a maximum follow-up of 31.7 years. All 64 primary PTCs were reclassified as T4a tumors according to the sixth edition of the UICC TNM classification of malignant tumors (2002) [17]. In the new TNM staging system, T4a carcinoma was defined as a tumor extending beyond the thyroid capsule and invading either subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve. Patients with bulky tumor considered clearly unresectable were excluded from the present analysis, as were patients who were found to have anaplastic carcinoma on postoperative histopathological examinations.

Thirteen patients underwent curative resection to entirely remove extensive invasion (complete surgery group). Five patients had tracheal deep invasion and eight patients had invasion extending to the larynx. The 13 resections included six pharyngolaryngoesophagectomies, two total laryngectomies, and five circumferential trachea resections. The six pharyngolaryngoesophagectomies were followed by reconstruction with a free jejunal graft. Eighteen patients did not consent to complete surgery because of the risk of functional impairment of the neck, especially the laryngeal function (incomplete surgery group). Fourteen patients had tracheal deep invasion and four patients had larynx invasion. Thrty-three patients with minimal invasion (no intraluminal or extremely limited invasion) underwent conservative resection with preservation intent (conservative surgery group). Twenty-nine patients had trachea invasion and four patients had larynx invasion, but all were superficial or limited invasions. The 33 conservative resections included 13 shave and 20 partial resections. The partial resections were 16 partial trachea resections and 4 partial laryngectomies by window or wedge resection.

The complete and conservative surgery groups underwent total thyroidectomy, whereas the extent of thyroid resection in the incomplete surgery group ranged from partial to total thyroidectomy. Ipsilateral or bilateral modified neck dissection (MND) was performed in all 13 complete and 30 conservative surgery group patients. Ipsilateral MND was systematic dissection of pretracheal and paratracheal central nodes and ipsilateral lateral nodes. Eighteen incomplete and the remaining three conservative surgery group patients individually underwent elective lymphadenectomy. Other neck structures such as the recurrent laryngeal nerve, spinal accessory nerve, esophagus, and internal jugular vein were excised at the same time in complete or conservative surgery when they were involved.

In complete surgery group, one patient who underwent circumferential trachea resection had bilateral recurrent laryngeal nerve (RLN) paralysis and permanent tracheostomy as surgical complication. Eight patients who underwent pharyngolaryngoesophagectomy or total laryngectomy had permanent tracheotomy in each surgical procedure. Seven patients had permanent hypocalcemia. Jejunal graft function was satisfied in all of six patients who underwent reconstruction after pharyngolaryngoesophagectomy. In incomplete surgery group, one patient had RLN paralysis and permanent tracheostomy as surgical complication. Permanent hypocalcemia did not occur in this group. In the conservative surgery group, RLN paralysis as surgical complication was not found; however, one patient underwent transient tracheostomy. Permanent hypocalcemia occurred in five patients.

The complete surgery group had no microscopic evidence of residual tumor after surgery. Surgical margins were pathologically negative in all. The conservative surgery group did not have any macroscopic disease, but there was suspicion of microscopic disease. Surgical margins were macroscopically negative in all, but were pathologically positive or unclear in seven patients. The incomplete surgery group had various degrees of macroscopic residual tumor. All 64 patients received thyroid-stimulating hormone (TSH) suppression as adjuvant therapy. External beam radiotherapy (EBRT) and radioactive iodine (RI) therapy were performed in selected patients, as shown in Table 1.

We compared clinical outcomes, recurrence, distant metastasis, and disease-specific survival (DSS) between the three groups. We also evaluated the influence of types of surgery

Table 1 Patients' characteristics and clinical outcomes

	Complete (n=13)	Incomplete (n=18)	Conservative (n=33)	P value
Gender (M:F)	4:9	4:14	9:24	0.8606
Mean age (years)	61.6	61.2	61.8	0.9861
Follow-up (months)	66.2	63.1	118.6	0.0196
Adjuvant therapy				
EBRT	0	7	2	0.0015
RI	0	1	1	0.6799
Local disease	6(46.2%)	18(100%)	7(21.2%)	<0.0001
Distant metastasis	6(46.2%)	14(77.8%)	4(12.1%)	<0.0001
Lung	4	7	4	
Bone	1	2	0	
Lung and bone	0	3	0	
Brain	1	1	0	
Skin	0	1	0	
Disease mortality	3(23.1%)	17(94.4%)	4(13.8%)	<0.0001
DSS rates				<0.0001
5-year	83.9%	44.4%	92.3%	
10-year	62.9%	11.1%	87.7%	
15-year	–	–	80.9%	

EBRT External beam radiation therapy, *RI* radioactive iodine, *DSS* disease-specific survival

(complete, incomplete, and conservative surgery) and invasion (tracheal deep, larynx, and minimal invasion) to DSS.

Statistical analysis

Means were compared by one-way ANOVA and multiple comparison test (Fisher's PLSD as post hoc test). Frequencies were compared with the chi-square test. DSS rates were evaluated with the Kaplan–Meier method and the log-rank test. The influence of surgery and invasion to DSS was evaluated by univariate analysis using the Cox proportional hazards models [Hazard ratio (HR), 95% confidence interval (CI)]. Differences were considered statistically significant when p values were less than 0.05. Statistical analyses were performed with Stat View-J, version 5.0.

Results

Table 1 shows the patients' characteristics and clinical outcomes. Gender ratio and mean age were similar between the three groups. Adjuvant EBRT was performed more in the incomplete surgery group than in the complete or conservative surgery group. Six (46.2%) complete and seven (21.2%) conservative surgery group patients had local recurrence, whereas all 18 incomplete surgery group patients had persistent disease. Six (46.2%) complete, 14 (77.8%) incomplete, and 4 (12.1%) conservative surgery group patients developed distant metastasis (P<0.0001). Three (23.1%) complete, 17 (94.4%) incomplete, and 4 (13.8%) conservative surgery group patients died of disease (P<0.0001). Distant metastases were the major cause of death in the complete surgery group, whereas both local and distant metastases frequently caused death in the incomplete surgery group. The 5- and 10-year DSS rates in the complete, incomplete, and conservative surgery groups were 83.9 and 62.9%, 44.4 and 11.1%, and 92.3 and 87.7%, respectively. The DSS curves differed significantly (P<0.0001), as shown in Fig. 1.

In Cox proportional hazard analysis, incomplete surgery significantly related to the increased risk of DSS (p<0.0001, HR 12.9, 95% CI 4.2–39.8) compared to conservative surgery, whereas complete surgery did not (p=0.1374). Tracheal deep invasion (p=0.0019, HR 7.6, 95% CI 2.1–27.0) and larynx invasion (p<0.0001, HR 9.9, 95% CI 3.1–31.6) significantly related to the increased risk of DSS compared to minimal invasion.

Table 2 summarizes previously reported survival rates in patients undergoing complete, incomplete, or conservative surgery for PTC with laryngotracheal invasion. In the Meta-analysis, the 5-year survival rates after incomplete surgery ranged from 35 to 50%, as compared with nearly 80% or higher after complete surgery. The 10- and 15-year survival rates after incomplete surgery were much worse. On the other hand, survival rates after conservative surgery were generally closer to those after complete surgery than after incomplete surgery. The outcomes in our complete and incomplete surgery groups were comparable to those in previous studies. The survival rates in our conservative surgery group seemed to be better than those in previous studies.

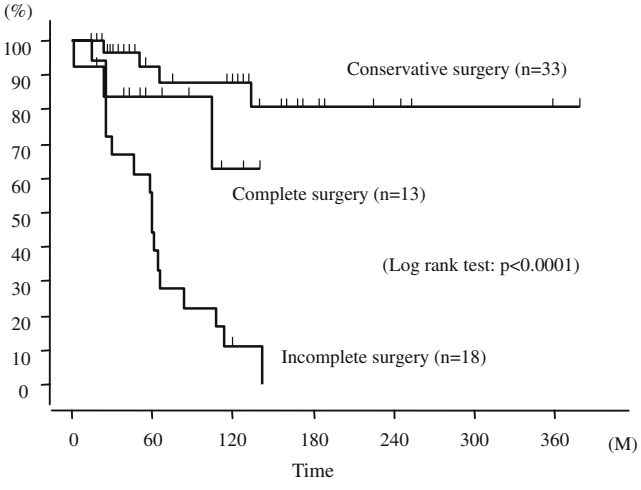

Fig. 1 The 5- and 10-year disease-specific survival rates in complete, incomplete, and conservative surgery groups were 83.9 and 62.9%, 44.4 and 11.1%, and 92.3 and 87.7%, respectively. The survival curves differed significantly (Kaplan–Meier methods, log-rank test, P<0.0001)

Table 2 The 5-, 10-, and 15-year disease-specific survival rates in patients with papillary thyroid carcinoma (PTC) with laryngotracheal invasion who underwent complete, incomplete, or conservative surgery

Author	No. of patients (PTCs)	Surgical modality	Survival rates (%)		
			5-year	10-year	15-year
Lipton et al. (1987) [10]	48(32)	Complete (n=14)	>90	>55	30
		Incomplete (n=14)	35	–	–
		Conservative (n=20)	>75	>55	40
Ishihara et al. (1991) [1]	60(49)	Complete (n=34)	78	78	–
		Incomplete (n=26)	44	24	–
McCaffrey et al. (1994) [13]	262	Complete (56% of cases)	79	63	54
Ballantyne (1994) [12]	46(30)	Complete (n=46)	>50	–	–
Nishida et al. (1997) [18]	117(108)	Complete to no resection	67–87 (for all)	–	–
McCarty et al. (1997) [14]	40(32)	Complete (n=5) and conservative (35)	–	84 (for all)	–
Czaja and McCaffrey (1997) [15]	124	Complete (n=34)	>85	>75	>75
		Incomplete (n=15)	50	50	>30
		Conservative (n=75)	>85	>70	>65
Nakao [8] 2001	31	Complete (n=31)	77	67	–
Our study	64	Complete (n=13)	84	63	–
		Incomplete (n=18)	44	11	–
		Conservative (n=33)	92	88	81

Some figures include the small numbers of patients with other histologic types of thyroid carcinoma

Discussion

We retrospectively analyzed the clinical outcome of different modes of resection in 64 primary PTCs with laryngotracheal invasion. Complete surgery has been a subject of controversy because of difficulty in maintaining a balance between disease cure and patients' quality of life. Our patients who underwent incomplete surgery were candidates for complete surgery, but refused to receive curative resection to avoid functional impairment of the neck, especially the laryngeal function. Thus, the patients undergoing incomplete surgery in our series were unlike those in previous studies. The present study found that survival was significantly better after complete surgery than after incomplete surgery, but our incomplete surgery group did not include clearly unresectable bulky tumors or anaplastic carcinomas.

Many authors [1–9] have recommended that locally advanced thyroid carcinomas should be treated by complete surgery to improve outcomes. However, extended radical resection and reconstruction may have serious complications. Omura et al. [9] concluded that pharyngolaryngoesophagectomy followed by reconstruction with a free jejunal autograft is a safe and reliable procedure. Complete surgery group patients in this study did not have any critical perioperative complications.

Conservative resection also remains a point of controversy. Our conservative group patients had favorable prognosis. Some authors [14, 15, 18, 19] have noted that the depth of infiltration of the trachea is an important determinant of outcome. Tovi and Goldstein [19] reported that intraluminal invasion carried a poorer prognosis than extraluminal cartilage invasion. Studies from the Mayo clinic have also demonstrated that intraluminal invasion indicates a poor prognosis [11]. Our results revealed that tracheal deep invasion (p=0.0019, HR 7.6) and larynx invasion (p<0.0001, HR 9.9) significantly related to DSS compared to minimal invasion. Thus, the depth of laryngotracheal invasion needs to be carefully evaluated [18]. Accurate diagnosis of the depth of invasion could be essential for conservative procedure.

McCaffrey and Lipton [11] recommended that partial laryngotracheal resection should be considered to preserve neck function. Another investigation by McCaffrey et al. [13] again found that nearly 50% of patients who had gross residual tumor survived for more than 5 years, with no significant difference in survival between patients receiving complete resection and those receiving shave resection. In our series, conservative resection for minimal invasion had a more favorable prognosis than incomplete resection. Our incomplete surgery group patients had macroscopic residual carcinoma to preserve neck function although complete resection was considered feasible, whereas conservative surgery group patients had either only microscopic or no carcinoma left behind after resection. A microscopically positive surgical margin may be acceptable. Kebebew and Clark [16] suggested that TSH suppression, EBRT, RI therapy, or a combination of these treatments are effective against microscopic residual disease. McCarty et al. [14] showed that conservative surgery with adjuvant radiotherapy achieved favorable prognosis. Only small numbers of our patients received adjuvant radiotherapies. We consider that more use

of adjuvant radiotherapies may have better outcomes in PTC patients with laryngotracheal invasion. This could be an important issue in our future clinical practice.

Others have opposed conservative resection. Park et al. [3] suggested that shave procedure was inadequate resection. Ozaki et al. [5] found that tracheal invasion had different longitudinal and circumferential patterns of spread and concluded that wedge resection was less effective than circumferential sleeve resection. Further studies are required to resolve the controversy regarding conservative resection procedures, created in part because the definition of conservative surgery ranges from only pathological involvement of the surgical margin to the presence of relatively gross residual tumor.

Locally advanced lesions can be the primary cause of disease-related mortality. Some investigators [19, 20] have reported that active local disease is closely associated with death from thyroid malignancy. Moreover, gross residual differentiated thyroid carcinoma may transform into undifferentiated carcinoma. We believe that local control should always be assigned the highest priority, irrespective of the presence or absence of distant metastasis. Our findings suggest that PTCs with laryngotracheal invasion can be treated with complete or conservative surgery according to the degree of tumor invasion, extensive or minimal.

Conclusion

The degree of tumor invasion is significantly related to survival. Complete surgery should primarily be considered for PTCs with laryngotracheal invasion. Patients in whom curative resection is feasible but who do not consent to complete surgery have disappointing outcomes. In addition, conservative surgery for minimal invasion is considered satisfactory to accomplish favorable prognosis.

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