CLINICAL STUDY

Macroscopic lymph-node involvement and neck dissection predict lymph-node recurrence in papillary thyroid carcinoma

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Abstract

Objective: Whether lymph-node dissection (LND) influences the lymph-node recurrence (LNR) risk in patients with papillary thyroid cancer remains controversial. The prognostic impact of macroscopic and microscopic lymph-node involvement at diagnosis is also an unresolved issue. A retrospective study was conducted to assess the influence of various LND procedures and to search for LNR risk factors.

Methods: Overall 545 patients without distant metastases prior to surgery and main tumour ≥ 10 mm were included. A total thyroidectomy was performed in all patients with either no LND (Group 1, $n = 161$), bilateral LND of the central and lateral compartments (Group 2, $n = 181$) or all other dissection modalities (Group 3, $n = 203$). Post-operative radioiodine was given to 496 (91%) patients. The 10-year cumulative probability of LNR was assessed and a prognostic study using multivariate analysis was performed.

Results: Macroscopic lymph-node metastases were present in 118 patients, 57 diagnosed before surgery and 61 only at surgery (including 81% in the central compartment). Overall, the 10-year cumulative probability of LNR was 7%. Macroscopic lymph-node metastases ($P = 0.001$), extra-thyroidal invasion ($P = 0.017$) and male gender ($P = 0.05$) were independent risk factors, while bilateral LND of the central and lateral compartments was protective ($P = 0.028$). In patients with macroscopic lymph-node metastases, the 10-year probability was lower in Group 2 than in Group 3 (10% vs 30%, $P < 0.01$). In patients without macroscopic lymph-node metastases ($n = 427$), no significant differences were observed between the three LND groups.

Conclusions: Patients with macroscopic, but not microscopic, lymph-node involvement have a major LNR risk and need an optimal LND at primary surgery.

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Introduction

Persistence or recurrence of lymph-node metastases (LNR) occurs in 5–20% of patients with papillary thyroid cancer (PTC) (1–4). The risk of LNR is generally higher in older patients, in patients with some histological subtypes (e.g. tall-cell variant) or with tumour extension beyond the capsule (extra-thyroidal invasion) (1, 5, 6). Macroscopic lymph-node metastases (7), and the number of node metastases and of capsular rupture (8), have also been shown to increase the risk of LNR. In contrast, the prognostic significance of microscopic lymph-node metastases remains unknown. Surgery is the main treatment of LNR. Consecutive LNRs may occur in a given patient, leading to repeated surgical resections, thereby affecting the quality of life. In some studies (1, 9), LNR was also shown to influence survival.

Routine lymph-node dissection (LND) and its extent is a subject of debate in PTC patients (10, 11). No studies

have assessed the long-term risk of LNR in patients with or without initial extensive LND. Over the past 30 years, three surgical approaches have been used in our demographic area, each applied in approximately one-third of patients: 1) no LND in the absence of macroscopic lymph-node involvement; 2) bilateral LND of central and lateral compartments when frozen section suggested PTC > 1 cm, whether or not macroscopic lymph-node metastases were present; 3) more limited LND based on the surgeon's policy and surgical findings.

The various surgical approaches, associated with the availability of a clinical database, offered a unique opportunity to assess both prognostic impact on LNR and complications, in a large series of patients with PTC. Our data also allowed us to investigate the respective roles of macroscopic and microscopic lymph-node metastases at diagnosis in the development of LNR, a currently unresolved issue.

Patients and methods

Patients

Patients with PTC ≥ 10 mm, treated by total thyroidectomy, without distant metastases detected beforehand, were included in the study. Diagnosis was based on the written pathological report. Overall, 545 patients were selected (Table 1). The male to female ratio was 0.26:1 and median age at diagnosis was 45 years. Macroscopic or microscopic extra-thyroidal invasion was found in 18% of patients. Distant metastases detected after thyroid surgery were found in 5% of patients. Median follow-up was 69 months (6 months to 36 years).

Surgical teams and procedures

Surgery was generally performed by head and neck surgeons at the Centre Baclesse Comprehensive Cancer Centre, by either head and neck, general or thoracic surgeons at the Caen University Hospital and by various specialists in other Basse-Normandie institutions.

Total thyroidectomy was performed in a single intervention in 396 (73%) patients, of whom 278 also

underwent LND. It was performed in two interventions in 149 patients, of whom 106 also had LND.

Several LND modalities were used. When there was no evidence of lymph-node involvement, before or during surgery, three main procedures were used: 1) no LND; 2) prophylactic LND including ipsilateral levels IIa, III, IV, VI (12) and contralateral levels III, IV, VI, with preservation of internal jugular vein, sternocleidomastoid muscle and accessory spinal nerve; 3) LND of various extent, from adenectomy to regular LND of the central and/or lateral compartment. In the context of macroscopic lymph-node metastases, LND (at least adenectomy) was always performed.

Patients were then categorized into three LND groups (Table 2): Group 1, no dissection ($n=161$); Group 2, bilateral LND of central and lateral compartments ($n=181$); Group 3, all other dissection modalities ($n=203$).

Criteria for initial lymph-node involvement

Lymph-node involvement was assessed by histological examination. Microscopic involvement was screened using standard pathological techniques. All nodes

Table 1 Patient characteristics and pathological features.

	All patients		Macroscopic lymph-node involvement				P value
			No		Yes		
Number of patients	545		427		118		
Gender							
Women	433	79%	349	82%	84	71%	0.015
Male to female ratio	0.26		0.22		0.40		
Period of diagnosis							
1965–1979	20	4%	9	2%	11	9%	0.002
1980–1989	78	14%	60	14%	18	15%	
1990–2003	447	82%	358	84%	89	76%	
Age at diagnosis years							
Median (range)	45	(7–96)	46	(7–87)	41	(17–96)	0.22
<20 years	20	4%	17	4%	3	2%	0.030
20–39 years	187	34%	134	31%	53	45%	
40–59 years	220	40%	184	43%	36	31%	
≥60 years	118	22%	92	22%	26	22%	
Neck dissection ^a							
Group 1	161	30%	161	38%	0		<0.001
Group 2 ^b	181	33%	121	28%	60	51%	
Group 3 ^c	203	37%	145	34%	58	49%	
Pathology							
Tumour size							
10–19 mm	227	42%	182	43%	45	38%	<0.001
20–39 mm	216	40%	183	43%	33	28%	
≥40 mm	102	18%	62	14%	40	34%	
Multifocal tumour	240	44%	172	40%	68	58%	0.001
Bilateral tumour	156	29%	111	26%	45	39%	0.011
Extra-thyroidal invasion	98	18%	53	12%	45	38%	<0.001
Distant metastases	28	5%	13	3%	15	13%	<0.001
Radioiodine ablation	496	91%	386	90%	118	93%	0.467
Cervical irradiation	18	3%	6	1%	12	10%	<0.001
Median follow-up months	69	6–440	68	6–332	72	6–440	0.192

^aGroup 1, no neck dissection; Group 2, dissection of ipsilateral levels IIa, III, IV, VI and contralateral levels III, IV, VI; Group 3, all other dissection modalities.

^bAmong the 121 patients with no macroscopic lymph-node involvement, 42 had microscopic involvement.

^cAmong the 145 patients with no macroscopic lymph-node involvement, 34 had microscopic involvement.

Table 2 Extent of neck dissection.

	All patients		Macroscopic lymph-node involvement	
	N		No	Yes
Group 1	161	30%	161	0
Group 2	181	33%	121	60
Group 3	203	37%	145	58
Level VI only	45	8%	36	9
Ipsilateral			16 (6) ^a	5 (1)
Contralateral			1	1
Bilateral			19	3
Lateral compartments only ^b	64	12%	45	19
Ipsilateral			13 (3)	14 (6)
Contralateral			1	0
Bilateral			31	5
Ipsilateral level VI and	33	6%	22	11
Ipsilateral compartments			9 (2)	6 (2)
Bilateral lateral compartments			13 (10)	5 (2)
Contralateral level VI and	19	3%	17	2
Ipsilateral compartments			1	1
Bilateral lateral compartments			16	1
Bilateral levels VI and	10	2%	7	3
Ipsilateral compartments			6	3
Contralateral compartments			1	0
Adenectomy	22	4%	14	8
Unspecified	10	2%	4	6

^aNumbers in brackets indicate patients with bilateral tumour.^bLevels III, IV ± IIa.

identified from dissection were cut into 2–3 mm sections that were all paraffin embedded; all sections were then screened for microscopic involvement. A lymph-node metastasis was considered macroscopic when clinically visible or palpable before or during surgery, according to written reports of the surgeon and pathologist. It was also considered macroscopic when suspected on preoperative ultrasonography (US), performed in 70% of patients treated since 1990. All other lymph-node metastases were considered microscopic.

Radioiodine (¹³¹I) treatment

A first therapeutic activity of ¹³¹I (median activity, 3.96 GBq) was given to 496 (91%) patients after withdrawal of thyroid hormone treatment, at a median interval of 2 months after surgery. A whole body scan (WBS), associated with static images centred on anterior neck, was performed 5 days after ¹³¹I administration. Post-¹³¹I WBS was considered abnormal when foci were visible outside the thyroid bed. At least a second therapeutic activity of ¹³¹I was given to 112 patients: in 28 patients with iodine-positive distant metastases; 30 patients with suspected locoregional residual disease; and 54 patients with persistent thyroid remnants after the first ¹³¹I treatment.

First year management after initial treatment

In patients treated with ¹³¹I and without suspected residual locoregional or distant disease ($n=438$), the

usual procedure to ensure total thyroid ablation was to perform, at 6–12 months, a diagnostic WBS after 185 MBq ¹³¹I, and to measure serum thyroglobulin (Tg) and anti-Tg antibodies (TgAb) on thyroid-stimulating hormone (TSH) stimulation. This procedure was done following withdrawal of thyroid hormone treatment ($n=306$) or recombinant TSH (Thyrogen, Genzyme Corp., Cambridge, MA, USA; $n=59$). Total thyroid ablation was also confirmed by negative post-therapeutic WBS in patients treated with at least two therapeutic activities of ¹³¹I ($n=54$). No evaluation was done at 6–12 months for the other 19 patients.

Long-term follow-up

Patients were followed-up on an annual basis, with neck palpation and serum-free thyroxine, TSH, Tg and TgAb assays under L-thyroxine treatment. Neck US was performed when neck palpation was doubtful or when Tg level ≥ 1 ng/ml.

Thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb)

Serum Tg measurements were performed in duplicate according to the manufacturer's instructions and results were reported as the average of duplicate values. RIA was used from December 1990 to April 2003 with the following kits: Tg-RIA Henning (Dade Behring Holding, Eschbom, Germany) from December 1990 to December 1996, RIA-Tg-S Behring from January 1997 to June

1998 and RIA-Tg-S Brahms (BRAHMS, Berlin, Germany) from July 1998 to April 2003. The immunometric assay Tg-Kryptor (BRAHMS) was used from May 2003 to December 2006. Serum TgAb were measured simultaneously using: Thytrak assay Behring from December 1990 to October 1998, TgAb DYNOTest (BRAHMS) from November 1998 to October 1999, TgAb Nichols Advantage (Nichols Institute Diagnostics, San Clemente, CA, USA) from November 1999 to August 2005, and Immulite TgAb (Diagnostic Product Corporation, Los Angeles, CA, USA) until December 2006.

Criteria for lymph-node recurrence (LNR)

LNR was defined as evidence of lymph-node metastases after completion of initial treatment. LNR was revealed by clinical or US examination and/or high levels of serum Tg and/or results of imaging, i.e. post-¹³¹I WBS or positron emission tomography (PET) using 18-F-fluoro-deoxy-D-glucose. Histological confirmation of LNR was made after surgery in all patients.

Surgical complications

Post-operative hypocalcaemia was defined as calcium serum values <2 mmol/l. Hypoparathyroidism was considered permanent when it required vitamin D analogues more than 6 months after surgery. Otherwise, hypoparathyroidism was considered transient.

Laryngeal nerve palsy was diagnosed by laryngoscopy in patients with post-surgical dysphonia. It was considered permanent when lasting over 6 months.

Statistical analysis

The cumulative probability of LNR was the main end point analysed. Patient characteristics were compared using Fisher's exact test, variance analysis or the Kruskal-Wallis non-parametric test, as appropriate. Time to LNR was calculated from the date of thyroid surgery to date of first LNR, date of last examination or 1 July 2004 (data update). The cumulative probability of LNR was calculated as 1 minus probability of surviving without developing LNR, estimated according to the Kaplan-Meier method. Rates between groups were compared using the log-rank test with or without adjustment on variables linked to LNR risk. Ninety-five percent confidence intervals (CI) for the rates were estimated using the Rothman and Boice method. A prognostic factor analysis was performed using the proportional hazards regression model, with LNR as dependent variable. Results were expressed using relative risks (RRs) and corresponding 95% CI. Independent variables were: gender, age at diagnosis (<40 vs 40–59 vs ≥60 years), tumour size (10–19 vs ≥20 mm), tumour multifocality (no versus yes), tumour bilaterality (no versus yes), extra-thyroidal invasion (no versus yes), distant metastases (absent versus

present), neck dissection (Group 1 versus Group 2 versus Group 3), lymph-node involvement (unknown or no involvement versus microscopic versus macroscopic involvement), cervical irradiation (no versus yes) and radioiodine ablation (no versus yes). Results were reported according to REMARK recommendations (13). Two-sided tests were used in reporting results. Statistical significance was defined as $P < 0.05$. Data, selected from files stored at the Clinical Research Unit, Centre François Baclesse, Caen, France, were analysed using STATA statistical software (release 8.2).

Results

Patient characteristics

Of the 545 patients, 161 had no LND (Group 1), 181 a bilateral LND of central and lateral compartments (Group 2) and 203 all other LND modalities (Group 3). Patients with LND (Groups 2 and 3) were more frequently males (23% and 24% vs 14%, $P = 0.010$), more often had extra-thyroidal invasion (17% and 24% vs 12%, $P = 0.015$) and more frequently underwent radioiodine ablation (97% and 92% vs 83%, $P < 0.001$). No differences were noticed on age and follow-up.

Macroscopic lymph-node metastases were present in 118 patients at diagnosis (22% of all patients and 31% of those with LND). Of the 118 patients with macroscopic node metastases, 57 were diagnosed before surgery (all localized in lateral compartments). In the other 61 patients, node metastases were found at surgery either in the central compartment ($n = 37$) or in lateral compartments ($n = 11$) or in both compartments ($n = 11$; localization was unspecified in two patients). Among the 427 patients without macroscopic involvement, 76 had microscopic lymph-node metastases (14% of all patients and 20% of those with LND). The proportion of lymph-node involvement in Group 2 was 56%: 33% were macroscopic and 23% microscopic. Characteristics of patients with or without macroscopic nodal metastases are reported in Table 1. Difference was statistically significant for all characteristics listed, excepting ¹³¹I treatment and follow-up.

Lymph-node recurrence (LNR)

Thirty-five patients (6%) developed at least one LNR leading to 10-year cumulative rates of 7.0% (95% CI, 5.0–9.9%; Table 3). Five patients (nos. 10, 12, 13, 16, 23) presented two consecutive LNRs and one (no. 25) underwent three operations because of persistent nodal disease. LNR occurred within 12 months following diagnosis in 16 out of 35 (46%) patients. Median time to relapse was lower in Group 1 (14.5 months) and Group 3 (12 months) than in Group 2 (45 months; $P = 0.047$).

Of the 35 patients, 6 were in Group 1, 5 in Group 2 and 24 in Group 3. Twenty-five patients initially showed

Table 3 Characteristics of the 35 patients who developed lymph-node recurrence.

Initial presentation and treatment																		
ID	Sex/ age	Diagnosis (month/ year)	Thyroid tumour location	Lymph-node involvement				First year management				Lymph-node recurrence			Last news at December 2006			
				Dissection modalities ^a	Nx/N0/N1 (micro/ macro ^b)	Location ^a	No. of nodes removed/ involved/ with capsu- lar rupture	I ¹³¹ ablation (yes/no)	Post I ¹³¹ WBS ^c	T or D activity of I ¹³¹	Post I ¹³¹ WBS	Tg off T ₄ (ng/ml)	Elapsed time since diagnosis (months)	Location ^a	Diagnostic methods ^d	Date (month/ year)	Status ^e	Tg (ng/ml) on T ₄ /after stimulation
Group 1																		
1	F/41	09/98	Bil		Nx			Yes	R	T	No RU	13	11	L Bil	Syst.Surg.	11/06	DF	<0.2/ND
2	F/87	08/98	Bil ^f		Nx			No					4	L & C Bil	Clin	06/99	Dead-rel.	—
3	F/27	12/81	Uni		Nx			No					200	L Ipsi	Clin	02/05	DF	<0.2/ND
4	F/75	10/87	Uni		Nx			No					18	L Ipsi	Clin	06/93	Dead-rel.	—
5	F/36	11/97	Bil ^f		Nx			Yes	R,N,L	T	N	27	16	L Ipsi	US,WBS*	06/06	DF	<0.2/4
6	M/25	12/97	Bil ^f		Nx			Yes	R	T	N	134	13	L & C Ipsi	WBS	08/01	DF	<0.2/0.6
Group 2																		
7	M/46	06/98	Bil ^f		N1/macro	C & L Bil	56/20/0	Yes	R,N	T	N,L	326	29	C Ipsi	WBS*	12/06	DF	0.2/ND
8	M/61	10/90	Bil ^f		N1/macro	L Ipsi	24/4/0	Yes	R	D	No RU	0	192	L Ipsi	US,PET	12/06	AD	0 ^g
9	F/36	02/99	Bil ^f		N1/macro	C & L Ipsi	16/5/0	Yes	R	T	No RU	9	48	L Ipsi	US,PET	12/06	DF	<0.2/<0.2
10	M/48	09/97	Bil		N1/macro	C & L Bil	26/21/12	Yes	R	T	No RU	1236	45	C Ipsi	Clin,PET	12/06	AD ^h	0.5/ND
11	F/28	04/02	Uni		N1/macro	C & L Ipsi	53/16/6	Yes	R,N	T	N	3 ^g	18	C Ipsi	US,PET	10/06	DF	<0.2/<0.2
Group 3																		
12	M/58	01/97	Uni	C Ipsi	N1/micro	C Ipsi	3/3/0	Yes	R	T	N	21	11	C Ipsi	WBS*	11/06	AD ^h	11/ND
13	F/34	02/02	Uni	C Ipsi	N0		NA/NA/NA	No					9	L & C Ipsi	Clin	06/06	DF ^h	0.5/2.3
14	F/28	01/92	Uni	C Ipsi	N0		NA/NA/NA	Yes	R	T	N	278	51	L & C Ipsi	US,WBS*	06/06	DF	<0.2 ^g /ND
15	M/46	01/98	Uni	C Bil	N0		NA/NA/NA	Yes	R,N	T	N	13	7	L Bil	WBS*	04/06	DF	<0.2/0.4
16	F/69	02/01	Uni	C Bil	N0		9/0/0	Yes	R	D	No RU	0 ^g	38	L Bil	Clin,US	10/05	Dead-rel ^h	
17	M/73	01/00	Bil ^f	L Ipsi	N1/micro	L Ipsi	8/3/0	Yes	R	T	No RU	3	21	L Ipsi	Clin,US	10/06	DF	NA
18	F/34	10/03	Bil	Adenectomy	N1/micro	C Ipsi	3/3/0	Yes	R	T	N	14	12	L & C Ipsi	WBS*	05/06	DF	<0.2/<1.0
19	M/32	06/98	Uni	C Ipsi	N1/macro	C Ipsi	1/1/0	Yes	R	T	No RU	23	8	L & C Ipsi	Syst.Surg.	03/06	DF	<0.2/1.8
20	F/37	06/93	Bil ^f	C Bil	N1/macro	C Bil	11/11/2	Yes	R	T	No RU	139	10	L Ipsi	Clin	08/06	DF	0.6/ND
21	F/67	09/80	Uni	L Ipsi	N1/macro	L Ipsi	5/2/2	Yes	R	T	No RU	NA	57	L Ipsi	Clin	10/86	Dead-unrel.	
22	F/34	10/00	Uni	L Ipsi	N1/macro	L Ipsi	7/3/0	Yes	R,N	T	N	6	6	C Ipsi	WBS*	09/06	DF	<0.2/<0.2
23	F/64	11/97	Bil	L Ipsi	N1/macro	L Ipsi	NA/NA/yes	Yes	R,N,L	T	N	265000	3	L & C Bil	Clin,WBS	09/06	AD ^h	8468/ND
24	M/81	11/96	Bil	Adenectomy	N1/macro	L Ipsi	1/1/1	Yes	R	T	No RU	6	36	L Ipsi	Clin,US	05/02	Dead-unrel.	
25	M/54	04/03	Uni	C Bil & L Ipsi	N1/macro	L Ipsi & C Con	10/3/3	Yes	R	T	N	768	12	L Ipsi & C Con	Clin,US, PET,WBS	11/06	AD ^h (Neck)	24/ND
26	F/72	12/90	Bil	L Ipsi	N1/macro	L Ipsi	7/7/0	Yes	R	T	No RU	3050	14	L Bil	Clin	04/93	Dead-rel.	
27	F/38	12/70	Uni	L Bil	N1/macro	L Bil	11/2/1	No					144	L Ipsi	Clin	03/03	DF	0.4/ND
28	M/64	03/85	Uni	Adenectomy	N1/macro	L Ipsi	NA/NA/NA	Yes	R	D	No RU	NA	23	L Ipsi	Clin	01/98	Dead-unrel.	
29	F/23	11/95	Bil ^f	C & L Ipsi	N1/macro	L & C Ipsi	8/6/2	Yes	R	T	No RU	327	10	L Con	Clin,US	08/06	DF	1.8/ND
30	F/78	10/02	Uni	C & L Ipsi	N1/macro	C Ipsi	17/8/0	Yes	R	T	No RU	166	15	L & C Ipsi	US	08/04	Dead-unrel.	
31	M/25	01/84	Uni	C Bil & L Ipsi	N1/macro	C Bil & L Ipsi	23/11/0	Yes	R,L	T	N,L	NA	12	L Ipsi	Clin	09/01	DF	0.2/ND

Initial presentation and treatment

 $\geq$ Two LNRS.

The strongest prognostic factor was macroscopic lymph-node involvement. Data were therefore analysed according to its presence or absence. Among 118 patients with macroscopic lymph-node metastases, the 10-year LNR cumulative probability, adjusted for gender and extra-thyroidal invasion, was 30% (95% CI, 22–48%) in Group 3 and 10% (95% CI, 4–24%) in Group 2 ($P<0.01$, Fig. 1A). In contrast, in the 427 patients without macroscopic lymph-node metastases, the 10-year adjusted rates were 3% (95% CI, 1–8%) in Group 1, 5% (95% CI, 2–11%) in Group 3 and 0% (95%

Table 4 Results of multivariate analysis on lymph-node recurrence: initial and final models ($n=545$).

Variable	Patients at risk	Initial model			Final model ($n=545$)		
		Relative risk	95% CI ^a	<i>P</i> value	Relative risk	95% CI ^a	<i>P</i> value
Gender							
Women	433	1.0			1.0		
Men	112	2.77	1.31–5.86	0.008	2.01	1.00–4.02	0.050
Age							
<40 years	207	1.0					
40–59 years	220	0.46	0.17–1.22	0.117			
≥60 years	118	1.35	0.57–3.17	0.496			
Tumour size							
<20 mm	227	1.0					
≥20 mm	318	1.29	0.60–2.77	0.521			
Tumour focality							
Unifocal	303	1.0					
Multifocal	240	2.16	0.77–6.06	0.144			
Tumour laterality							
Unilateral	385	1.0					
Bilateral	156	1.46	0.54–3.93	0.459			
Extra-thyroidal invasion							
No	447	1.0			1.0		
Yes	98	2.12	0.99–4.53	0.054	2.39	1.17–4.88	0.017
Distant metastases							
No	517	1.0					
Yes	28	0.70	0.23–2.12	0.526			
Neck dissection							
Group 1	161	1.0			1.0		
Group 2	181	0.20	0.04–1.01	0.052	0.18	0.04–0.83	0.028
Group 3	203	1.08	0.29–4.10	0.908	0.78	0.22–2.79	0.703
Lymph-node involvement							
Unknown/no involvement	351	1.0 ^b			1.0		
Microscopic involvement	76	1.72	0.37–8.07	0.490	1.64	0.36–7.53	0.525
Macroscopic involvement	118	7.17	2.26–22.69	0.001	7.22	2.36–22.08	0.001
Cervical irradiation							
No	527	1.0					
Yes	18	0.22	0.05–1.03	0.055			
Radioiodine ablation							
No	49	1.0					
Yes	496	0.34	0.11–1.02	0.054			

^a95% CI denotes 95% confidence interval.^bReference category includes patients with no lymph-node involvement and those without neck dissection.

CI, 0–20%) in Group 2 ($P=0.12$, Fig. 1B). In these 427 patients, multivariate analysis showed that extra-thyroidal invasion (RR=8.06; 95% CI, 2.69–24.2; $P<0.001$) was associated with increased risk of LNR, while radioiodine ablation was associated with low risk (RR=0.25; 95% CI, 0.08–0.81; $P=0.021$).

Surgical complications

The proportion of transient post-operative hypoparathyroidism was higher in Group 2 than in other groups ($P<0.001$; Table 5). However, no significant differences in permanent hypoparathyroidism were observed between the three LND groups, or between Groups 2 and 3 ($P=0.17$). Concerning post-operative transient or permanent laryngeal nerve palsy, no statistical differences were observed between the three LND groups in patients with or without macroscopic lymph-node metastases.

Discussion

In a retrospective series of 545 patients with PTC ≥ 10 mm originating from the Basse-Normandie

Figure 1 Cumulative probability of lymph-node recurrence according to lymph-node dissection adjusted for gender and extra-thyroidal invasion: (A) patients with macroscopic lymph-node involvement (adjusted log-rank test: $P=0.01$); (B) patients without macroscopic lymph-node involvement (adjusted log-rank test: $P=0.12$). Group 1, no neck dissection; Group 2, dissection of ipsilateral levels IIa, III, IV, VI and contralateral levels III, IV, VI; Group 3, all other dissection modalities.

area in France, the LNR rate was limited to 7% at 10 years. Almost half of LNRs occurred in the year following diagnosis suggesting that most patients with LNR had persistent disease rather than true recurrences. The presence of macroscopic, but not microscopic, lymph-node involvement is the strongest risk factor for LNR while a bilateral dissection of central and lateral compartments is associated with lower risk at multivariate analysis. As previously reported, extra-thyroidal invasion (1, 5, 6, 14–16) and male gender (1, 5, 6, 15, 17) are also related to an increased risk.

The present data clearly show that the effects of LND differ in patients with and without macroscopic lymph-node metastases. In patients with macroscopic metastases, the cumulative probability of LNR at 10 years is 10% in those who underwent dissection of central and lateral compartments (Group 2), and 30% in those undergoing all other dissection modalities (Group 3). These findings are in accordance with previous studies, where in patients with enlarged nodal metastases, systematic LND resulted in a lower recurrence rate and better survival than selective lymph-node removal (3, 18). In contrast, the probability of LNR is $<5\%$ in patients with no macroscopic lymph-node metastases, whatever the extent of LND. Similar results were reported in patients with papillary microcarcinoma (19). This low risk of LNR contrasts with the substantial proportion of patients (approximately one-fourth) who presented with initial microscopic nodal involvement. One can assume that the progression of such microscopic disease is slow and not detectable for decades. Another explanation is that the disease is eradicated by LND and/or radioiodine ablation. The absence of LNR in Group 2 patients and the 'protective effect' of radioiodine ablation on multivariate analysis, support this hypothesis. However, the real impact of radioiodine treatment on LNR remains controversial (6, 20–22). In patients who undergo an optimal treatment and who have a negative evaluation at 6–12 months, and are therefore considered at low risk of recurrence, these results make us question the utility of repeating tests to detect LNR on a long-term basis. Finally, the distinction between microscopic or macroscopic nodal disease appears neither in the tumour node metastasis (TNM) classification for thyroid cancer (23) nor in other prognostic systems such as AMES (15), AGES and MACIS (14). Our results suggest that better identification of these groups would be helpful.

A major controversy is whether a dissection of the central neck compartment should be routinely performed in patients with PTC (10, 11). In our series, macroscopic nodal metastases were found at surgery in 10% of patients, most of them (80%) located in the central compartment. These patients clearly benefit from LND whereas those with only microscopic involvement may not. One difficulty is to assess preoperatively the presence of lymph-node involvement

Table 5 Surgical complications according to neck dissection.

	Group 1 (no dissection)		Group 2 (bilateral dissection of central and lateral compartments)		Group 3 (all other dissection modalities)		Total		P value
All patients	161		181		203		545		
Hypoparathyroidism									
Transient	7	4%	29	16%	12	6%	48	9%	<0.001
Permanent	3	2%	12	7%	7	3%	22	4%	0.077
Laryngeal nerve palsy									
Transient	6	4%	7	4%	11	5%	24	4%	0.778
Permanent	2	1%	3	2%	4	2%	9	2%	0.917
Patients without macroscopic lymph-node involvement	161		121		145		427		
Hypoparathyroidism									
Transient	7	4%	20	17%	9	6%	36	8%	0.001
Permanent	3	2%	8	7%	5	3%	16	4%	0.111
Laryngeal nerve palsy									
Transient	6	4%	2	2%	6	4%	14	3%	0.550
Permanent	2	1%	2	2%	1	1%	5	1%	0.859
Patients with macroscopic lymph-node involvement	—		60		58		118		
Hypoparathyroidism									
Transient	—	—	9	15%	3	5%	12	10%	0.126
Permanent	—	—	4	7%	2	3%	6	5%	0.680
Laryngeal nerve palsy									
Transient	—	—	5	8%	5	9%	10	8%	1.0
Permanent	—	—	1	2%	3	5%	4	3%	0.360

with acceptable sensitivity and specificity. A recent study suggests that it could be missed at preoperative US in about half the cases, even in experienced hands (24). It should also be highlighted that post-operative radioiodine is less effective on macroscopic tumours. Finally, unlike surgery for lateral recurrence, re-operation for central recurrence is associated with high morbidity (25). This presents an argument for the systematic (i.e. 'en bloc') dissection of the central neck. Although central LND, as performed in Group 2 patients, is associated with the highest rate of permanent hypoparathyroidism, the risk remains limited (7%), under the care of experienced surgeons. Prospective studies are needed to assess the predictive value of preoperative methods, such as conventional or functional imaging, in detecting central macroscopic nodal disease. This would help to limit central LND only to patients who would benefit from it.

Once macroscopic central node metastases are detected at surgery, the extent of LND in the lateral compartments is a subject of discussion. In the case of unilateral thyroid tumour, some practitioners advocate the dissection of the ipsilateral compartment. Our results show that the probability of contralateral recurrence is up to 20%. Therefore, the decision to dissect both ipsi- and contralateral compartments should take into account the high probability of cure in a limited proportion of patients and surgery-related inconveniences (longer operation, cosmetic and painful

sequels) for all. When thyroid tumour is bilateral, dissection of both lateral compartments appears to be indicated at first attempt as previously suggested (26).

This retrospective study allows for potential bias and limitations. First, although it covers a long period (1965–2003), where improvements in imaging and biological technology may have resulted in differences in the likelihood of detecting recurrences, the vast majority of patients (82%) were diagnosed after 1990, at a time where the main tools of surveillance, i.e. US and serum Tg measurements, were used routinely in our patients. Secondly, although it facilitated data analysis, our *a posteriori* categorization into three dissection groups can be considered as arbitrary. In particular, Group 3 encompasses a wide range of procedures, from a single adenectomy to more extensive dissection, which probably do not have an equivalent impact on nodal recurrence. Finally, post-operative radioiodine was administered in most, but not in all patients, and this can introduce a potential bias. These differences in treatment modalities have been taken into account in multivariate analysis.

In conclusion, this study confirms that in patients with PTC, macroscopic lymph-node metastases are a major risk factor for LNR; it also provides evidence of the limited influence of microscopic nodal disease. Finally, this study outlines the need for adequate LND in patients with macroscopic lymph-node metastases detected before or at surgery.

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