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Prognostic Factors Associated with the Survival of Patients Developing Loco-Regional Recurrences of Differentiated Thyroid Carcinomas

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To estimate survival of patients with loco-regional recurrences (LRRs) of differentiated thyroid carcinomas (DTCs) and to identify factors associated with survival after LRRs, we analyzed retrospective data of the 172 patients treated and followed up in our institution from 1958 to 2000 who had developed LRRs (6% of DTC patients). Ultrasound, when used, picked up 95% of the recurrences. Survival was estimated with the method of Kaplan-Meier, and associated prognostic features were studied in univariate and multivariate Cox model-based analyses. Cumulated survival rates 10 yr after LRRs were 49.1, 89.3, and 32.1% for all patients, patients aged less than 45 yr, and older patients, respectively. Multivariate analysis identified three features related to initial tumor (age ≥ 45 yr, follicular histology, presence of thyroid capsular effraction), the absence of radioiodine ablation of thyroid remnants after initial surgery (10% of patients did not receive radioiodine), the presence of distant metastases before LRR diagnosis, and two features related to the LRRs (no radioiodine uptake and thyroid bed location) as significantly associated with a reduced survival. Our results underline the seriousness of LRRs of DTCs and could be used to identify patients who should benefit from a closer follow-up and especially reactive therapeutic intervention. (*J Clin Endocrinol Metab* 89: 5362–5368, 2004)

PATIENTS WITH DIFFERENTIATED thyroid carcinomas (DTCs) are usually considered as having a good prognosis and a near normal life span (1–5). However, the disease may have an aggressive course and 5–27% of patients with DTCs develop loco-regional recurrences (LRRs) of the tumor (1, 3, 6–10). Such recurrences have been reported to be located in cervical lymph nodes in 60–75% of cases, thyroid bed in about 20% of cases, and trachea or muscle in about 5% of cases (3), worsening the prognosis and leading to a risk of cancer-related death (6, 11–15).

Several prognostic factors of recurrences (often including both distant metastases and LRRs) have been proposed, including age, male gender, tumor size, local tumor invasion or regional lymph node metastases, follicular histology, partial thyroidectomy, and absence of radioiodine remnant ablation treatment (1, 6, 8, 16–19). In contrast, studies that provide estimates of survival rates in patients presenting with LRRs (6, 8, 16, 20) or that examine prognostic factors associated with the survival of such patients remain limited (7, 10, 20–22). Most of the studies did not distinguish local from distant metastases (10, 21, 22) or did not include a multivariate analysis (7, 21).

The aim of our study was to estimate survival of patients with DTC LRRs and identify prognostic factors associated with survival in a series of 172 patients treated and followed up in our institution for DTCs with LRRs. To our knowledge, our study is the only one available to date that combines the following three characteristics: the study is specific of LRRs, is based on an appropriate survival-based multivariate analysis, and includes a large number of patients. Such an approach could be used to identify patients who should benefit from a closer follow-up.

Patients and Methods

Patients

Among the 3124 patients with DTCs that were treated and followed at the Department of Nuclear Medicine of the Groupe Hospitalier Pitié-Salpêtrière from 1958 to 2000, 177 (6%) developed LRRs that were diagnosed during the follow-up after initial treatment. Information concerning patients was obtained from their medical records. Follow-up information and date of death were obtained either from the medical records or from town council registers. Because follow-up information was unavailable for five of the 177 patients, the final study population included 172 patients (109 women and 63 men). The mean age at diagnosis of local recurrence was 53 yr (range 14–89, median 57). At the end of the study, 57 (33%) patients had died, 29 of them from their thyroid cancer, 14 of them from another cause. The cause of death was unknown for 14 patients.

Abbreviations: DTC, Differentiated thyroid carcinoma; LRR, loco-regional recurrence; Tg, thyroglobulin; WBS, whole-body scan.

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Initial treatment and follow-up

Initial treatment of DTCs included total or near-total thyroidectomy (for 157 and 15 patients, respectively) and lymph node surgery (modified radical lymph node dissection in 84 patients, limited lymph node excision in 21 patients), completed by an ablative ^{131}I dose of 100 mCi after surgery (162 patients). For a long time, radioiodine ablation has depended on the result of the diagnostic whole-body scan (WBS) performed 6 wk after surgery. Nine of the 10 patients who did not receive initial radioiodine ablation were treated for their initial tumor before 1975. Four patients had no cervical uptake and then no radioiodine ablation, two had a cervical radiotherapy instead of radioiodine, one had initial lobectomy and late completion thyroidectomy, one presented with an iodine overload, and one had a Hurthle cell tumor. The medical chart of the last patient did not mention the rationale for the absence of radioiodine ablation. All patients were thereafter subjected to T_4 treatment at suppressive dose. Histological data were obtained from initial pathological reports, and cases were not reviewed. The size of the initial tumor was available for 133 patients (mean size 40 mm; range 5–120 mm), and 17 of them presented with a microcarcinoma (tumor 10 mm or smaller). The staging of the primary tumor, according to the tumor nodes metastases classification (23), was assessable in 132 patients: 33 (25%), 31 (23.5%), 49 (37.1%), and 19 (14.4%) were presenting with a T1, T2, T3, and T4 tumor stage, respectively. Regional lymph node metastases were present in 106 cases (61.6%). Distant metastases were initially present in eight patients (4.7%).

Follow-up protocol consisted in regular clinical examination, chest radiographs and thyroglobulin (Tg) detection (systematically performed since its availability in 1981). First appointment 6 months after radioiodine ablation also included WBS under TSH stimulation (withdrawal of T_4 or more recently, use of recombinant human TSH) to check the efficiency of thyroid remnant ablation. Subsequent check-ups were performed under TSH stimulation 12 months later and every 3 yr during 7 yr and then, with suppressive treatment, every 3 yr. Many changes in the follow-up of patients with DTCs and/or LRRs have occurred when considering the period of the study. For instance, WBS diagnostic tool progressively appeared less useful (24) and has been replaced, in our department, by systematic WBS 5 d after radioiodine treatment. Since 1997 ultrasonography is systematically performed before radioiodine ablation and has replaced preradioiodine WBS diagnostic tool (25). Conversely, ultrasonography and fine-needle aspiration biopsy were progressively included in the follow-up since 1988, and both techniques are now major tools in combination with recombinant human TSH-stimulated thyroglobulin test (26, 27). Mean follow-up was 8.3 yr (range 8 months to 35.4 yr, median 6.8 yr). Ninety-five percent of patients had a delay between initial treatment of primary tumor and diagnosis of recurrence less than 10.4 yr (mean 3.3 yr; range 4 months to 21.5 yr; median 1.9 yr). Such results may not reflect the present situation, routine neck ultrasonography allowing a potential early discovery of neck recurrences.

Definition and diagnosis of LRR

LRR was defined as a thyroid bed, soft tissues, or cervical lymph node recurrence of an initial treated DTC. Patients who were both once retreated by ^{131}I within 6 months after initial treatment for an isolated cervical positive ^{131}I uptake without Tg elevation and did not present any other loco-regional abnormality afterward were not considered in our study. In the literature, the underlying sense of the term recurrence is highly variable. Currently surgical report, preablative ultrasonography, and post-radioiodine ablation WBS are tools that may help to distinguish between persistent and recurrent disease. However, such a distinction remains frequently difficult, closely related to the diagnostic methods used to detect the recurrence that changed during the course of our study. In our series, two patients presented a recurrence within 6 months after initial surgery, despite the fact that one of them had benefited from a total surgery, a modified radical cervical lymph node dissection, and radioiodine ablation.

LRR was suspected by clinical examination, ^{131}I positive uptake in the cervical area, elevated Tg level (>10 ng/ml), or abnormal features at ultrasonography. LRR detection was clinical in 62% of cases (cervical or lymph node palpation, more rarely dysphonia or dyspnea) and represented 80% of the diagnoses before 1981, 50% after 1981.

LRRs were discovered by clinical examination in 104 patients (60%), a positive uptake at WBS and/or an elevation of Tg level in 52 patients (30%), and ultrasonography in 12 patients (7%). The medical records of the four remaining patients did not allow the identification of the initial tool used to diagnose the recurrence. Ultrasonography was performed in 61 patients (35%) and localized the recurrence in 58 of them; Tg level was measured in 108 patients and was elevated in 84 (78%) of them. One hundred patients benefited from both WBS and Tg measurement, and 54 of them (54%) presented with both a cervical positive radioiodine uptake and an elevated Tg level, whereas 12 (12%) presented both a negative radioiodine uptake and a Tg level less than 10 ng/ml under TSH stimulation.

The diagnosis of LRR was assessed by histological analysis at surgery for 114 patients (66%), positive ^{131}I cervical uptake after ^{131}I diagnostic (11.1 MBq) or therapeutic (3.7 GBq) dose for 55 patients (32%), and fine-needle aspiration biopsy for three patients.

Statistical analysis

Survival curves were estimated with the Kaplan-Meier method using SPSS statistical software (SPSS Inc., Chicago, IL). We considered initial time as the date of recurrence treatment, such a date corresponding to a standardized reliable proof of recurrence for all patients. Final time was defined as the date of either death or last news from survivors (censored cases).

The following variables were studied: age at primary tumor diagnosis (<45 or ≥45 yr old), age at the diagnosis of LRR (<45 or ≥45 yr old), sex, period of initial diagnosis (earlier than 1980 or 1981 or later), period of recurrence diagnosis (earlier than 1980 or 1981 or later), time between initial cancer surgery and recurrence, histological type of initial tumor (papillary/follicular), initial tumor size (<40 mm, ≥40 mm), invasion of initial tumor (multifocality, thyroid capsular invasion, vascular invasion, extrathyroid extension of the tumor), complete initial surgery (total or near-total thyroidectomy *vs.* partial thyroidectomy), initial cervical lymph node surgery (modified radical lymph node dissection or limited lymph node excision *vs.* no lymph node surgery), initial radioiodine therapy (yes/no), recurrence location (lymph node only, thyroid bed only, both localizations), radioiodine uptake of recurrence (yes/no), Tg level elevation (yes/no), histology of recurrence (differentiated, poorly differentiated), initial lymph node metastases (yes/no), distant metastases before recurrence diagnosis (yes/no), distant metastases after recurrence (handled as a time-dependent variable), surgical treatment of the recurrence (yes/no).

Because several changes in the follow-up of patients with DTCs have occurred, when considering the period of the study (24, 26), some of the studied variables were unavailable for some patients. Such a situation yields problems for a standard multivariate analysis resulting in two alternative strategies: either not include some variables (those with missing data) in the analysis or perform the analysis considering only the patients with no missing data. To overcome this problem, we used the recommended technique of multiple imputations (28, 29). Such a technique is based on a Bayesian approach and consists of replacing missing data by a sample of best guess-simulated data. In practice, we assigned 10 imputations to each missing datum using the *aregImpute* function implemented by Frank Harrell in the R statistical software (30). The prognostic value of each variable for survival was studied separately in an univariate analysis using Cox proportional hazard model. The resulting confidence intervals and P values took into account the multiple imputations, when necessary. A variable with $P < 0.05$ was considered significantly associated with the survival function. Variables in the univariate analysis presenting $P < 0.20$ were entered into a multiple regression Cox analysis with backward elimination of variables to identify a small set of variables with independent prognostic significance. Again, the multivariate analysis took into account the potential multiple imputations. All Cox-based analyses were performed using R statistical software (30).

Results

The overall survival of the patients is shown in Fig. 1. The results of univariate analyses are shown in Table 1 (patient and primary tumor characteristics, initial treatment) and Table 2 (recurrence characteristics, distant metastases).

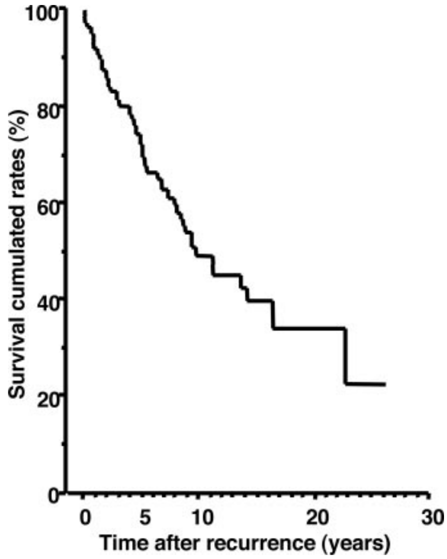

FIG. 1. Overall survival of patients with LRRs originating from DTCs. Initial time was considered as the date of LRR diagnosis.

Overall survival

The overall survival rates (all causes of death) after LRRs at 5, 10, and 20 yr were, respectively [estimate (95% confidence interval)], 69.8% (61.0%–77.9%), 49.1% (38.5%–59.8%), and 34.1% (20.6%–49.2%), with a median survival of 9.8 yr (mean 13.1 yr). Survival of men and women appeared similar. There was a nonsignificant trend of improved survival among patients whose initial tumor or recurrence was treated after 1981 (Tables 1 and 2). Survival was significantly improved among patients aged less than 45 yr at the time of initial tumor treatment or at the time of recurrence. For example, survival rates at 5, 10, and 20 yr for patients aged younger than 45 yr at the time of recurrence were, respectively, 92.7% (82.3–99.0%), 89.3% (77.1–97.5%), and 76.6% (49.2–96.1%), whereas the corresponding figures for patients aged 45 yr or older were, respectively, 58.2% (46.1–69.2%), 32.6% (21.2–45.0%), and 18.3% (6.0–34.9%).

The survival in the group of 29 patients who died from their thyroid cancer was not significantly different from the survival of the group of the remaining 28 patients who died ($P = 0.23$).

Characteristics and treatment of initial tumor

As shown in Table 1, survival was significantly improved in patients with primary papillary tumors ($P < 0.001$). Patients with large-sized tumors (≥40 mm) were not associated with a significant reduced survival ($P = 0.14$). Median time between initial treatment and recurrence diagnosis in the group of patients presenting with a tumor size less than 40 mm appeared similar to that of the group of patients presenting with a tumor size greater than 40 mm ($P = 0.99$ using a nonparametric test). Considering the 17 patients (9.7%) presenting with a microcarcinoma, three died, all from a thyroid cancer-related cause. A large-size tumor was observed in 16 and 34% patients with papillary and follicular tumors, respectively. Because these two proportions were significantly different ($P = 0.013$), primary tumor histological type and size did not appear as independent variables.

Considering invasion criteria, vascular invasion, capsular effraction, and extrathyroid extension were significantly associated with a reduced survival, whereas multifocality and initial cervical lymph node extension were not.

Considering the initial surgical treatment, total or near total thyroidectomy and modified radical or limited lymph node dissection were two features not associated with survival. In contrast, survival was significantly improved in the group of patients subjected to an ablative ^{131}I dose of thyroid remnants after primary thyroid surgery.

Characteristics of LRRs

As shown in Table 2, the delay between primary tumor diagnosis and recurrence was not significantly associated with survival. A WBS-positive ^{131}I uptake in the cervical area was associated with a significant improved survival, whereas the absence of Tg level elevation was not. Patients presenting with recurrences in the thyroid bed (41%) had a significantly reduced survival, compared with patients presenting recurrences only in lymph nodes (59%).

LRR surgery was not associated with survival ($P = 0,69$). Among the 114 patients with recurrences confirmed by surgery, 104 (91%) presented with a well-differentiated histological type, seven (6%) presented with a poorly differentiated type, and three (3%) presented with a thyroid tumor tissue but with no more details in the patient pathological chart. The presence of a poorly differentiated type was a feature significantly associated with a reduced survival.

The lung was the most frequent site of distant metastases and concerned 38 of the 49 patients with distant metastases. Bone metastases were diagnosed in 16 patients. Distant metastases were diagnosed before and after LRRs in 22 and 27 patients, respectively (Table 2). The presence of distant metastases before LRRs was significantly associated with a reduced survival ($P < 10^{-4}$).

Prognostic variables: multivariate analysis

The results of the Cox multivariate analysis are summarized in Table 3. Follicular histological type of primary tumor ($P < 0.004$), capsular effraction ($P < 0.002$), absence of radioiodine ablation of the thyroid remnants ($P = 0.03$), age of 45 yr or more at diagnosis of primary tumor ($P < 0.001$), and presence of distant metastases before the diagnosis of LRR ($P < 10^{-4}$), presence of the LRR in the thyroid bed ($P < 10^{-5}$), and no LRR radioiodine uptake ($P < 0.08$) were significantly associated with a reduced survival. When considering the event as the cancer-specific cause of death (29 deaths) instead of death from all causes (57 deaths), the final results of the multivariate analysis did not substantially change (data not shown).

Discussion

The prevalence of LRRs in patients with DTCs observed in our series (6%) is in the lower range of those previously reported in other studies (5–27%) (1, 3, 6–9, 11, 13, 21, 22, 31, 32). The observed discrepancies between studies are likely to

TABLE 1. Prognostic factors of survival after LRR: patient characteristics, primary tumor characteristics, and initial treatment [univariate analysis (Cox model)]

Studied variable	No. of patients (%)	Relative risk of death[a]	P
Age at primary tumor diagnosis (yr)			$<2 \times 10^{-5}$
<45	64 (37)	1	
≥45	108 (63)	5.75 (2.60–12.73)	
Period of initial diagnosis			0.10
<1981	63 (37)	1	
≥1981	109 (63)	0.63 (0.36–1.09)	
Sex			0.46
Female	109 (63)	1	
Male	63 (37)	1.23 (0.72–2.09)	
Histological type			0.001
Papillary	133 (77)	1	
Follicular	39 (23)	2.55 (1.50–4.35)	
Primary tumor size (mm)[b]			0.14
<40	77 (58)	1	
≥40	56 (42)	1.63 (0.85–3.13)	
Vascular invasion			0.027
No	128 (74)	1	
Yes	44 (26)	1.89 (1.07–3.33)	
Thyroid capsular effraction			0.002
No	119 (69)	1	
Yes	53 (31)	2.40 (1.39–4.16)	
Extrathyroid extension			0.003
No	122 (71)	1	
Yes	50 (29)	2.32 (1.34–4.00)	
Multifocality			0.47
No	111 (65)	1	
Yes	61 (35)	0.81 (0.46–1.43)	
Initial cervical lymph node metastases			0.18
No	66 (38)	1	
Yes	106 (62)	0.69 (0.41–1.17)	
Surgical treatment of initial tumor			0.94
Total or near-total	157 (91)	1	
Partial	15 (09)	1.04 (0.44–2.43)	
Initial cervical node surgery[c]			0.52
Yes	105 (61)	1	
No	67 (39)	1.19 (0.71–2.00)	
Radioiodine ablation of thyroid remnants			0.007
Yes	162 (94)	1	
No	10 (06)	3.08 (1.37–6.9)	

[a] Numbers in *parentheses* correspond to the 95% confidence interval.
[b] Data were unavailable for some patients and handled with multiple imputations.
[c] Includes modified radical lymph node dissection and limited lymph node excision.

be due to differences in the population studies and the diagnostic and inclusion criteria. Nevertheless, the beneficial impact of initial extensive surgery including total or near total thyroidectomy on the rate of tumor recurrence is well documented (6, 33, 34). In that regard, the low prevalence observed in our study may be due, in part, to such a surgical management of DTCs that had been advocated since the three last decades in our institution (35).

However, despite the infrequent occurrence of LRRs, our results emphasize the potential seriousness of such relapses and urge clinicians to identify patients with a higher risk of death. In our study, 57 patients (33%) died during follow-up. Several studies have evaluated mortality rates of patients with recurrence of DTCs but did not always take into account the different lengths of follow-up among patients. The reported death rates ranged from 15 to 38% (7, 8, 10, 21, 22, 32). The studies of Tubiana *et al.* (16) and Ortiz *et al.* (8) are the only ones in which a cumulated survival rate at 10 yr was calculated in patients with recurrence of DTCs. The respective rate estimates, 62 and 68% at 10 yr, are slightly better than the 49% estimate derived from our study. The observed discrepancies may be due to differences in the study populations and, in any case, are difficult to interpret.

As shown in Table 3, our Cox model-based multivariate analysis identified seven prognostic factors: an age 45 yr or more at the diagnosis of primary tumor, a follicular histological type, a thyroid capsular effraction of the primary tumor, the presence of distant metastases before diagnosis of LRR, the absence of radioiodine ablation of thyroid remnants after initial surgery, the presence of the recurrence in the thyroid bed, and the absence of radioiodine uptake of the recurrence. These were independent factors significantly associated with a reduced survival. It has to be noted that the implementation of multiple imputations allowed us to identify the absence of radioiodine uptake of the recurrence and the presence of the recurrence in the thyroid bed, two features with missing data, as significantly associated with a reduced survival in the multivariate analysis.

In our study, relative risk of death appears 5 times greater for patients aged at least 45 yr and 3 times greater for patients with

TABLE 2. Prognostic factors of survival after LRR: recurrence characteristics and distant metastasis [univariate analysis (Cox model)]

Studied variable	No. of patients (%)	Relative risk of death[a]	*P*
Age at recurrence (yr)			$<10^{-4}$
<45	59 (34)	1	
≥45	113 (66)	7.03 (2.80–17.66)	
Period of recurrence diagnosis			0.1
<1981	50 (29)	1	
≥1981	122 (71)	0.63 (0.37–1.09)	
Time between primary tumor diagnosis and recurrence (yr)			0.36[b]
<3	108 (63)	1	
3–6	33 (19)	1.81 (0.97–3.36)	
≥6	31 (18)	1.20 (0.60–2.41)	
Radioiodine uptake of recurrence[c]			0.04
No	63 (44)	1	
Yes	80 (56)	0.53 (0.29–0.97)	
Tg level elevation[c]			0.71
No	24 (22)	1	
Yes	84 (78)	1.18 (0.51–2.71)	
Histology of recurrence[c]			0.04
Well differentiated	104 (94)	1	
Poorly differentiated	07 (06)	3.53 (1.11–11.21)	
Localization of recurrence[c]			
Lymph node only	83 (59)	1	
Thyroid bed only	41 (29)	5.05 (2.62–9.74)	$<10^{-5}$
Both localizations	16 (12)	4.35 (1.85–10.22)	0.001
Distant metastases before diagnosis of recurrence[c]			$<10^{-4}$
No	146 (86)	1	
Yes	22 (14)	3.78 (2.06–6.93)	
Appearance of distant metastases after diagnosis of recurrence[d]			0.1
No	145 (84)	1	
Yes	27 (16)	1.90 (0.90–4.02)	
Surgery of recurrence			0.69
No	58 (34)	1	
Yes	114 (66)	0.89 (0.52–1.54)	

[a] Numbers in *parentheses* correspond to the 95% confidence interval.
[b] Tendency test.
[c] Data were unavailable for some patients and handled with multiple imputations.
[d] Time-dependent variable.

follicular tumors. Age and histological types were previously highlighted by Asakawa *et al.* (10) and Tubiana *et al.* (16), whose studies were based on a Cox multivariate model and by other univariate studies for age (7, 21). Follicular subtypes have been also reported as significantly correlated with mortality in patients with recurrences of DTCs (7, 10, 21). Nevertheless, changes in histological criteria for the diagnosis of malignancy, especially for follicular forms, have occurred in the three last decades (36). Such changes led to an increase in papillary cancers at the expense of encapsular and/or follicular forms. This tendency to overdiagnose the follicular variant of papillary thyroid carcinoma (37) may have resulted, in our study, in a lower estimation of the relative risk of death of patients with follicular cancers than the estimation that would result from a current review of the oldest pathological slides.

Our results further indicate that invasion criteria of the primary tumor have a significant impact on survival after LRRs. In our univariate analysis, tumors with vascular invasion, thyroid capsular effraction, or extrathyroid extension are associated with a 2-fold increased risk of death. Considering such features, thyroid capsular effraction was the only one that remained significantly associated to prognosis in the multivariate analysis. Asakawa *et al.* (10) did not confirm in their multivariate analysis the negative impact of local tumor extension found in the univariate analysis, and they did not find any role of distant metastases as prognostic factor. However, their study includes only 68 patients, and the results of the analyses may reflect some weakness in terms of statistical power.

Tumor size is a known prognostic factor in DTCs (1, 3, 6, 13, 14, 18). This feature was not significantly associated with survival in our study, neither in the univariate analysis nor in the multivariate analysis. Moreover, our study indicates that the delay between primary tumor and LRR does not depend on tumor size. In our series, three of the 17 patients with microcarcinomas died, all from cancer-related cause. These three patients all initially had follicular, multifocal, and invasive tumors (T3N0 for one, T3N1 for one, and T1N1 for one) (23). Although these cases confirm the previously reported fatal course of some patients with microcarcinomas, our rare observations should not be used to advocate for routine ablation with radioiodine in case of microcarcinoma (38).

Concerning initial treatment, our study indicates that initial radioiodine therapy is associated with an improved survival ($P < 0.02$). The beneficial impact of such a therapy on global survival has been previously reported (1, 3, 6, 16, 21, 32, 39). In our study, patients with a total thyroidectomy had a similar survival to that of patients with a partial thyroidectomy. The extent of surgery has been previously reported as a major factor associated with survival (5, 6, 33), but such results were based on the follow-up of standard cohorts of DTCs. Incomplete treatment may lead to a late diagnosis of recurrences and thus to a poor outcome. Therefore, our ap-

TABLE 3. Prognostic factors of survival after LRR: significant variables in the multivariate analysis (Cox model)

Studied variable	Relative risk of death[a]	P
Age at primary tumor diagnosis (yr)		<0.001
<45	1	
≥45	4.77 (1.88–12.10)	
Histological type of primary tumor		<0.004
Papillary	1	
Follicular	2.79 (1.41–5.52)	
Thyroid capsular effraction of primary tumor		<0.002
No	1	
Yes	2.77 (1.49–5.14)	
Radioiodine ablation of thyroid remnants after initial surgery		<0.03
No	1	
Yes	0.34 (0.13–0.86)	
Distant metastases before diagnosis of recurrence		$<10^{-4}$
No	1	
Yes	4.03 (2.08–7.83)	
Localization of recurrence[b]		$<10^{-5}$
Lymph node only	1	
Presence in the thyroid bed	4.76 (2.45–9.23)	
Radioiodine uptake of recurrence[b]		0.008
No	1	
Yes	0.40 (0.21–0.78)	

[a] Numbers in *parentheses* correspond to the 95% confidence interval.
[b] Data were unavailable for some patients and handled with multiple imputations.

parently contradictory results may be due to the fact that they are based on a particular high-risk patient group. More likely, because of the surgery practice evolution, only few patients (9%) were subjected to a partial thyroidectomy, the resulting statistical test being weak in terms of power.

Distant metastases were reported as the main cause of death from DTC (1, 3, 13, 14, 18, 40). Our study extends such results to the particular group of patients with DTC recurrences. We observed that the presence of distant metastases before the diagnosis of LRR is a valuable bad prognostic factor. The relative risk of death was 3.3-fold increased for patients with distant metastases appearing before LRR. Among the 22 patients with distant metastases before the neck recurrence, 15 died, eight of them from their thyroid carcinoma, whereas the specific cause of death could be linked to the neck recurrence itself in five of the eight cancer-related deaths. It could be argued that association between risk of death and histological type is due to distant metastases that would be more frequent in the case of follicular tumors. However, we checked the absence of interaction between these two factors. We observed that nine of the 27 patients with distant metastases diagnosed after LRR had died at the end of the study. This feature, although not significant in the multivariate analysis, was close to the threshold value. Our results suggest that appearance of metastases after LRR diagnosis is a prognosis feature likely not detected in our study because of a too rare number of cases.

Our data allowed us to analyze some factors related to the nature of the recurrence. We observed that recurrences located in the thyroid bed were associated with a 5-fold greater risk of death than those located in the cervical lymph node only. Grant *et al.* (15) previously underlined the bad prognosis of patients with a recurrence located in the thyroid bed. More recently, Mazzaferri and Kloos (6) reported that the 30-yr cancer mortality rate of patients with recurrence in the neck soft tissue (30%) was twice as high as that observed in patients with recurrences in cervical lymph nodes or the controlateral thyroid (16%, $P < 0.05$). We also observed that recurrences presenting a positive radioiodine uptake were associated with an improved survival. Our results are in accordance with those of Casara *et al.* (41), who previously reported the bad prognosis associated with metastatic foci that had lost their capacity to take up radioactive iodine.

We expected to have better survival rates for patients treated more recently, reflecting the beneficial impact of advances in diagnosis and treatment. In fact, we did not detect any significant difference between survival rates over four periods of time since 1958. We may lack the statistical power to detect such differences, and medical progress may be too recent to be assessable. In that regard, the fact that recurrences were discovered in only 12 patients by ultrasonography should be viewed in terms of the retrospective design of our study and contrasts with the fact that the recurrence was localized in 58 of the 61 patients who benefited from ultrasonography. It will be important in the future to investigate the impact on survival of current follow-up tools such as neck ultrasonography, ultrasound-guided fine-needle aspiration biopsy, and positron emission tomography especially relevant for patients with nonfunctional LRRs (42). In any case, diagnosis or treatment procedures, when detected as prognostic features, should be considered with caution. In the field of DTC pathology, *a fortiori* of LRRs, recommendations are mostly based on retrospective studies, such as the present one, and not derived from randomized trials (5, 6, 43). Many reasons, such as the rarity of LRRs or the close dependence between current treatment strategies and LRR patterns, make such trials impracticable.

Despite the usual favorable course of DTCs, our study underlines the reduced survival of patients presenting with LRRs. As assessed by multivariate analysis, the follicular histological type of the primary tumor, the presence of a thyroid capsular effraction, an absence of radioiodine ablation of thyroid remnants, an age of 45 yr or more at the diagnosis of primary tumor, the presence of distant metastases before the diagnosis of LRR, and two features related to the LRR (no radioiodine uptake and thyroid bed location) all appeared as independent prognostic features associated with reduced survival in patients with LRR of DTC.

Our results indicate that young patients presenting with isolated papillary lymph node metastases may relatively comfort the clinician but also confirms a long-standing intuitive clinical impression: elderly patients presenting LRR with the bad prognostic features detected in our study have an aggressive disease leading to frequent fatal outcome. Therefore, the prognostic factors evidenced in our study can be used to identify these patients with a higher risk of death. Such patients should benefit from a closer follow-up and especially reactive therapeutic intervention. Early management of such patients, using ultrasonography, fine-needle aspiration biopsy, and TSH-stimulated Tg measurement, may improve the prognosis. However, the generalized spread of such tools is relatively too recent in terms of estimating their precise impact on the survival of patients presenting with LRRs of DTCs. Further studies focused on such evaluations must be undertaken.

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