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Differentiated Thyroid Cancer With Liver Metastases: Lessons Learned From Managing a Series of 14 Patients

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Liver metastases from differentiated thyroid carcinoma (LMDTC) are rare and usually occur in disseminated metastatic disease. The aim of this study was to review the diagnosis and management of LMDTC. Between 1995 and 2011, 14 patients with a mean age of 59.7 years (+/-10.2) were treated for LMDTC. Data were retrospectively reviewed and analyzed. Seven patients had distant metastases at diagnosis, including 2 with synchronous liver lesions. The average time of onset of LMDTC from initial diagnosis was 52.2 months (+/49.5). All LMDTC were discovered during routine radiologic monitoring. Histologic analysis confirmed LMDTC in 5 patients. Eight patients received tyrosine kinase inhibitors, 1 patient underwent resection of their LMDTC after chemotherapy. Six patients (disseminated metastases, significant comorbidities) did

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not receive any specific treatment. The median survival after diagnosis of LMDTC was 17.4 months (+/-3.3): 23.6 months (+/-2.9) for patients who underwent chemotherapy versus 3.9 months (+/-0.9) for patients who did not receive any specific treatment ($P < 0.001$). Developing DTC liver metastasis is a very poor prognostic sign. Chemotherapy by TKIs, especially, hold promise in the cure of LMDTC for selected patients.

Key words: Liver metastasis – Thyroid carcinoma

Differentiated thyroid carcinoma, encompassing follicular and papillary carcinomas, has a good prognosis and long-term survival rates. Indeed, the 10-year survival rate is 80–95%. The incidence of distant metastases at the time of initial presentation of differentiated thyroid carcinoma (DTC) is 4%. During the course of treatment and follow-up, the prevalence of distant metastases ranges from 2% in low-risk patients, to 33% in high-risk patients. Distant metastases occur primarily in the lungs and, to a lesser extent, in bones. The presence of distant metastases is the most significant prognostic factor and is associated with poor outcomes. Only 50% of patients survive 10 years after a diagnosis of the metastatic DTC.[1–3]

Liver metastases from differentiated thyroid carcinoma (LMDTC) are rare, with a reported frequency of 0.5%. They tend to occur during the terminal phase of the disease are a grave event. Survival ranges from 1 to 60 months after diagnosis of LMDTC in the largest series of 11 cases.[4]

Because of this rarity, there is little information available on the diagnosis and management of LMDTC. We have therefore undertaken a retrospective, multicenter study on LMDTC and analyzed factors affecting survival.

Patients and Methods

Data source

We undertook a collaborative study between 7 academic thyroid centers. All consecutive cases of LMDTC were included. The study period varied between centers according to the local databases: Angers, 1995–2011; Geneva, 2005–2011; Marseille, 1995–2011; Paris, 2000–2011; Limoges, 2004–2011. The data of all patients who were diagnosed with LMDTC were retrospectively reviewed.

Patients

All patients were initially treated and monitored according to international recommendations. During follow-up, patients underwent the following investigations: serum thyroglobulin measurement, whole body scintigraphy, and cervical ultrasonography. Additional abdominal ultrasonography and/or CT were performed depending on the location of metastases and in cases of inconclusive scintigraphy in the context of a raised serum thyroglobulin. When possible, biopsies were performed.

Statistics

Parameters with normal distribution are expressed as mean ± standard deviation (SD). Parameters with skewed distribution are expressed as median and interquartile range (IQR). Comparisons between groups were made using analysis of variance (ANOVA). Survival rates were analyzed using the Kaplan–Meier method and groups were compared using the log-rank test. P values <0.05 were considered statistically significant. SPSS software version 11.0.1 SPSS, Chicago, IL, USA) was used for statistical analysis and to generate graphs.

Results

Study population

Fourteen patients were included in the study (6 females, 8 males). The mean age at diagnosis of DTC was 59.7 years (+/−10.2). Four patients presented with goiters, 6 with thyroid nodules, 2 with suspect lymph nodes, 1 with bone pain, and 1 with arm monoplegia. All of the patients underwent a total thyroidectomy for their primary thyroid malignancy. None of the patients had a history of cancer other than thyroid cancer.

Surgical technique

Five patients underwent central and lateral neck dissection and 7 underwent central neck dissection at the time of total thyroidectomy. One patient had 2 further operations for central lymphadenectomy at 2 and 3 years after initial surgery (thyroidectomy with central neck dissection). Nine patients had distant

Table 1 Treatment and survival of patients with liver metastases

Patients	DTC	Stage TNM	Average time of LMDTC appearance Months	I131 therapy before LMDTC appearance Number of sessions	Surgery	Chemotherapy	Survival After LMCDT diagnosis Months (months of follow-up)
1	*Mixted c.*	T3N1M1	45	4	-	-	6
2	*Follicular c.*	TxNxM1	156	9	+	+	18
3	*Papillary c.*	T1N0M1	120	6	-	-	1
4	*Follicular c.*	T1NxM0	5	0	-	-	3
5	*Follicular c.*	T1N0M1	125	4	-	+	Alive (6)
6	*Insular c.*	T3N1M0	51	2	-	+	16
7	*Papillary c.*	T3N1M1	55	5	-	+	28
8	*Papillary c.*	T3NxM1	0	0	-	-	3.5
9	*Papillary c.*	T1N1M0	64	2	-	+	Alive (11)
10	*Follicular c.*	TxNxM0	48	9	-	+	Alive (28)
11	*Follicular c.*	T2NxM0	25	3	-	+	Alive (21)
12	*Papillary c.*	T3NxM1	5	1	-	-	Alive (4)
13	*Follicular c.*	T4NxM1	0	1	-	-	Alive (9)
14	*Papillary c.*	T3N1M0	32	3	-	+	Alive (3)
Median			52	3.5			17

metastases at diagnosis including 2 with LMDTC associated with bone or pulmonary metastases.

Circumstances of LMDTC discovery

LMDTC were diagnosed by a thyroglobulin test elevation associated with liver lesions on imaging studies. All patients had elevated serum thyroglobulin. Among the 14 patients, 6 had cervical lymph node at the LMDTC discovery. Eleven cases of LMDTC were discovered on computed tomography (CT), 2 on FDG-PET, and one on Iodine 123 scintigraphy. Liver metastases (LM) appeared during a mean period of 52.2 months (+/− 49.5) after the initial treatment of the primary thyroid malignancy. Liver biopsy confirmed LM in 5 patients. None of the patients had a history of cancer other than thyroid cancer. We could not have histologic evidence of liver metastases of differentiated thyroid cancer in 9 patients. The diagnosis of liver metastases was established on the association between elevated thyroglobulin and imaging studies (PET, MRI, CT scan, scintigraphy) showing a tumor lesion appearance.

Therapeutic management of LMDTC

Most (n=13) patients received extensive treatment by Iodine 131 therapy (the mean dose of radioiodine therapy was 330 mCi, with an average of 3.5+/−2.9 sessions). Twelve patients received iodine-therapy after the initial neck surgery. One patient received iodine-therapy after LMDTC diagnosis. Eight patients received targeted chemotherapy with tyrosine kinase inhibitors during the course of their disease for LMDTC (1 vandetanib, 1 sunitinib, 1 pazopanib, and sorafenib, including 1 with a switch for sunitinib). None patient received other chemotherapy treatment. These 8 patients were all diagnosed with LM after January 2005. One patient underwent a liver resection (tumorectomy of the junction of liver segments V and VII) after chemotherapy and survived 18 months after hepatectomy. Six patients did not receive chemotherapy: 2 patients had bilobar liver involvement and chemotherapy was deemed not useful because of multi metastatic liver, 1 patient had a duodenal invasion and chemotherapy was considered dangerous (due to risk of perforation), 1 patient was in an altered general condition.

Two patients presented with LMDTC at end of the study period: in 1 patient, imaging studies showed progression of the LMDTC over a 9-month period and therefore he did not receive chemotherapy, and the other patient was recently diagnosed with LMDTC and follow-up imaging studies are awaited before starting chemotherapy.

Table 1 shows the initial stage of the thyroid cancer, the timing of LMDTC diagnosis and the treatment of LMDTC. Seven patients died of the LMDTC within 10.7 months[1–28] after the diagnosis of the LMDTC. Seven patients are still alive after a median follow-up of 11.7 months.[3–28] The median survival was 17.4 months (+/− 3.3). Patients who had chemotherapy had a significantly longer median survival than patients who did not have

Table 2 Comparison between chemotherapy group and no chemotherapy group

Groups	Sex	Age years	T	Initial staging N	M	Average time of LMDTC appearance months	Survival months
Chemotherapy group							
n = 8	4F/4M	55	1 Tx 3 T1 1 T2 2 T3 1 T4	3 N1	3 M1	69 [32–156]	28 Median : 23
No chemotherapy group							
n = 6	1F/5M	52	2 T1 4 T3	4 Nx 1 N0 1 N1	1 Mx 1 M0 4 M1	29 [0–120]	4 Median : 4

chemotherapy (23.6 +/− 2.9 months and 3.9 +/− 0.9 months respectively, $P < 0.001$; Table 2).

Fig. 1 shows a Kaplan–Meier representation of survival after LMDTC diagnosis according to treatment with TKI or not. Fig. 2 shows the evolution of patient 11 of Table 1 with LMDTC (21 months of follow-up, still alive at the end of the study with a stabilization of LMDTC).

Discussion

Interest of lifetime follow-up for young patients with long life expectancy

LMDTC are very rare, sometimes with a later onset.[5–7] Kouso *et al* reported a case of LMDTC diagnosed 32 years after thyroidectomy for follicular carcinoma.[5] In our series, mean time of onset of first liver metastases of DTC was 52 months and the longest delay was 13 years.

Interest of serum thyroglobulin and radioiodine scintigraphy in LMDTC screening

Serum thyroglobulin is unreliable in detecting liver metastases as patients often have metastases in multiple sites. Liver metastases from DTC can be detected by a variety of imaging modalities, such as ultrasonography, CT, and scintigraphy. Diffuse versus focal radioiodine accumulation in liver must be carefully distinguished. Only focal accumulation is characteristic of functional liver metastasis in which iodine uptake by cancerous cells is preserved. The correspondence of focal accumulation of radioiodine on whole-body scintigraphy with "cold" area on liver scintigraphy is specific for diagnosis of this metastasis. Radioiodine scintigraphy is a useful diagnostic tool in all patients as it also has therapeutic implications. If the radioiodine scintigraphy is positive, it confirms that radioiodine therapy can be both promising and successful.[8] If negative, the usefulness of radioiodine therapy is questioned. Unfortunately, LM does not normally accumulate radioiodine because of a dedifferentiation process. Therefore, scintigraphy alone is not enough for the detection of those metastases and whole-body CT and/or FDG PET should also be employed.[9–15] FDGPET is especially effective in detecting patients with elevated thyroglobulin levels and normal radioiodine whole-body scintigraphy. Dong *et al* reported a sensitivity and specificity of 93.5% and 83.9% respectively for distant metastases.14 In our study, all LMDTC were detected by elevated thyroglobulin serum. Eleven LMDTC (78.5%) were found on computed tomography (CT), 2 on FDG-PET. Figs. 1 and 2 show computed tomography and 18FDGPET liver lesions. Only 1 iodine scintigraphy was positive.

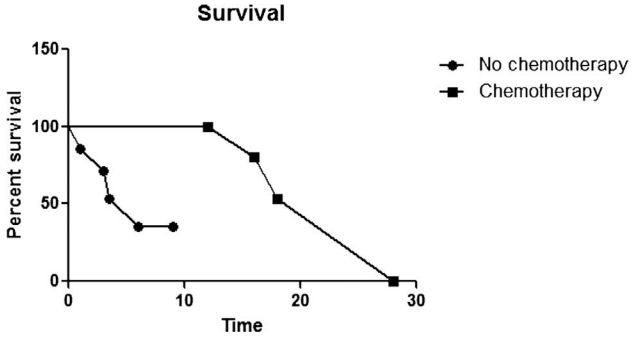

Fig. 1 Kaplan-Meier representation of survival after LMDTC diagnosis according to treatment with TKI or not.

Specific therapeutic management for LMDTC metastases

Liver surgery

Another difficulty is establishing a specific therapeutic management for these liver metastases. Surgery offers the best chance for long-term survival

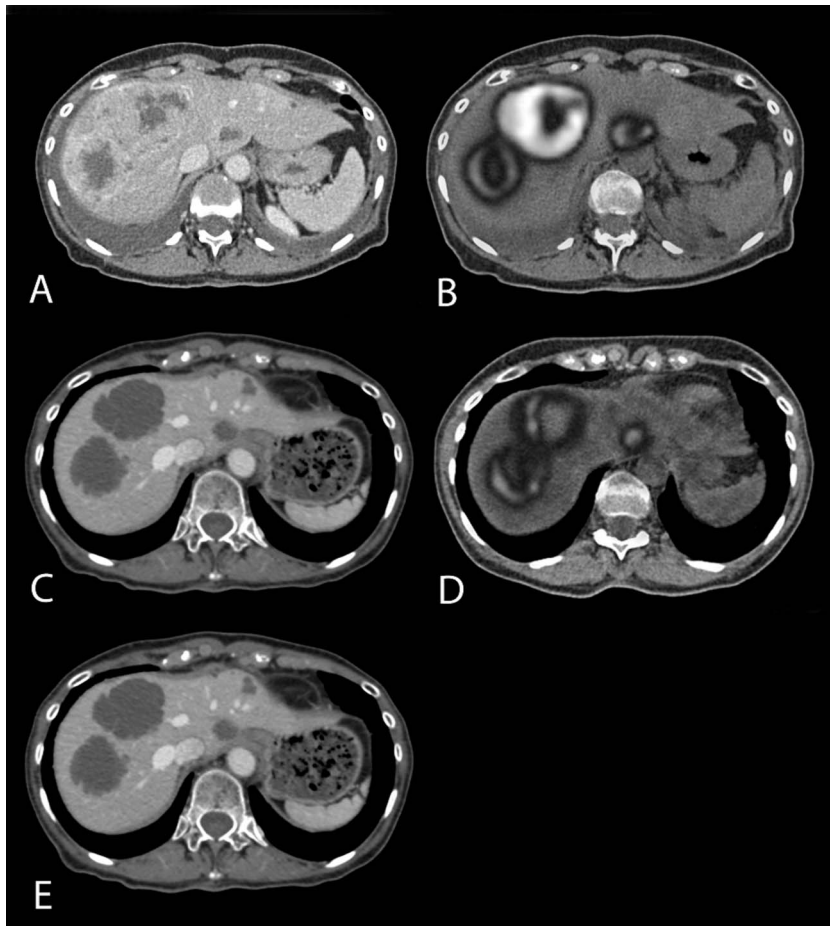

Fig. 2 This shows the evolution of patient 11 of Table 1 with LMDTC.A + B: Injected CT (A) and fused FDG-PET-CT (B) showing 3 LMDTC with an intense metabolic activity (mean SUV 15.7, max 32 for the biggest LM in this view). Thyroglobulin level was 93395 μg/L.C + D: Injected CT (C) and fused FDG-PET-CT (D) 6 weeks after treatment with the TKI pazopanib, at an initial dosage of 800 mg/d showing mainly necrotic/cystic changes of the LM, with a clear decrease of the metabolic activity (mean SUV of 3.4, max 8.1 for the biggest LM in this view).D: Injected CT 7 months after LMDTC diagnosis under a maintenance dosage of 400 mg/d of pazopanib, showing a stabilization of the LM. Thyroglobulin level was also stabilized at 11,903 μg/L.

according to a case report.[16] However, most patients are not eligible for surgery either due to multiple LMDTC not accessible to complete surgical excision, disseminated metastases, or because of significant comorbidities. In our series, only 1 patient was suitable for complete surgical excision of LMDTC with curative intent after chemotherapy with TKI. Unfortunately he died 18 months after surgery. The cause of death was pneumonia secondary to a pancytopenia caused by iodine therapy.

Radioiodine therapy

Radioiodine therapy is limited by dedifferentiation process (decreased expression and/or function of the sodium iodide symporter). It has been suggested that retinoids have beneficial effects on iodide uptake. Bexarotene treatment may partially restore I-131 uptake in some, but not all, metastases of DTC.[17,18] A recent study showed that selective mitogen-activated protein kinase increases in iodine uptake and retention in a subgroup of patients with thyroid cancer that is refractory to radioiodine. The effectiveness may be greater in patients with RAS-mutant disease.[19] In our series, 1 patient has been treated with retinoids and then with chemotherapy. This patient was still alive at the end of the study, 6 months after the diagnosis of LMDTC. In cases of functional LM, Gugliemi *et al* suggest a combination of percutaneous interstitial laser photocoagulation treatment and radioiodine therapy to avoid the side effects of 131I-therapy in thyrotoxic patient and to increase the effectiveness of radioiodine-induced neoplastic tissue ablation.[20]

Systemic targeted chemotherapy: tyrosine kinase inhibitor effectiveness

Finally, there are no studies on the effectiveness of a specific systemic chemotherapy for LMDTC. Angiogenesis is a major characteristic of tumor cells. Several factors, including VEGF (vascular endothelial growth factor), promote the development of a new blood supply at the primary tumor and metastases.[21] In thyroid cancer, a high level of

expression of VEGF is correlated with a higher tumor diameter, an increased rate of locoregional and distant metastasis and decreased disease-free survival.[22] VEGF targeting by different tyrosine kinases inhibitors (TKI) showed growth inhibition of papillary thyroid cancer.[23] In our study, 8 patients received chemotherapy-all received a tyrosine kinase inhibitor. This treatment was considered effective in 4 patients: 5 patients were still alive at the end of the study, including 1 with metastatic progression and 3 partial responses, 3 patients died (1 because of pancytopenia secondary to iodine therapy, 2 because of multimetastatic disease).

In this study, we found a significantly prolonged survival for patients who received TKI chemotherapy (28 months) compared to patients who did not receive TKI (4.75 months). Only patients without significant comorbidities could benefit from chemotherapy, which may represent a bias. In addition, tumor aggressiveness may vary depending on the type of cancer and explain this difference in survival. However, the age of the patients and the extent of the disease were similar in both groups.

Previous studies have demonstrated the efficacy of various TKIs in progressive differentiated thyroid cancer of follicular origin (nonmedullary thyroid cancer).[24–28] In the study by Sherman *et al*, 24 of the 93 patients had LMDTC[24,25] and in the study by Kloos *et al*, 8 of the 41 patients had "liver, kidney or adrenal metastases".[28] The proportion of patients with LM was not indicated in the study by Cohen *et al*,[26] which included 60 patients, and in the study by Gupta *et al*,[27] which included 30 patients. None of these studies described the evolution of patients with LMDTC but all showed more than two-thirds response rate (81% stable disease and partial response lasting for 6 months at least in Sherman *et al* study, 71% stable disease and partial response lasting for 6 months at least in Kloos *et al* study, 68% stable disease and partial response lasting for 16 weeks at least in Cohen *et al* study, and 76% stable disease and partial response lasting for 14 weeks at least in Gupta *et al* study) with LMDTC.

Some limitations and biases may affect our study's findings. Although our study appears to be one of the biggest cohorts assembled in the literature of this uncommon phenomenon, the small number of patients in this retrospective study does not allow definitive conclusions about the efficacy of TKI in LMDTC to be made. However, the apparent improved prognosis of patients treated with TKIs suggests that this type of chemotherapy should be envisaged when a patient is diagnosed. A prospective study, with a bigger cohort and a liver biopsy for all patients, is necessary to confirm our conclusion.

Conclusion

Metastases to the liver appear to be an advanced manifestation of metastatic thyroid cancer in association with other metastatic sites. This study shows that patients with DTC, who are most often young, should have regular follow-up over their lifetime. Because of a dedifferentiation process, most cases of LMDTC do not uptake iodine, therefore limiting the effectiveness of radioiodine therapy. Targeted chemotherapy show promising results in patients with LMDTC; however; larger studies are needed to confirm this preliminary data.

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