Patterns of metastasis in follicular thyroid carcinoma and the difference between early and delayed presentation

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ABSTRACT

INTRODUCTION Follicular thyroid cancer (FTC) has a good prognosis if treated early. The aim of this study was to look at the difference in outcomes in those who presented with metastasis early or late in their disease.

METHODS A retrospective cohort study was conducted of patients diagnosed with FTC ($n=91$) treated between 2000 and 2013. Demographic, laboratory, pathological and survival data were collected and analysed.

RESULTS Metastatic FTC was diagnosed in 20 cases (22%). The median age at diagnosis was 65 years (range: 17–86 years) and 65% of the patients were female. Twelve patients (60%) were diagnosed with metastatic disease at presentation, with the bones being the most common site (75%). In the remaining eight cases (40%), metastasis developed at a median of 4.5 years (range: 2–8 years) after initial thyroid surgery, lungs being the most common site (50%).

Eighteen patients (90%) underwent surgical intervention for the primary disease. Sixteen patients (80%) received adjuvant radioactive iodine and eight (40%) received external beam radiotherapy. Widely invasive follicular cancer was the predominant histological diagnosis (90%). No prognostic association was observed with any of the parameters studied. The overall disease specific mortality rate was 40%. There was no significant difference in mortality between those who presented with metastatic disease and those who developed metastasis during the follow-up period (33% vs 50%, $p=0.61$).

CONCLUSIONS The clinical outcome and prognosis for cases with metastatic disease is generally poor. Despite this, almost half of the patients in our study were still alive at a median follow-up of 5.5 years, regardless of whether they were diagnosed with metastatic disease on initial presentation or whether they developed metastasis after initial thyroid surgery.

KEYWORDS

Follicular – Thyroid – Cancer – Thyroidectomy – Radioiodine – Radiotherapy

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Follicular thyroid cancer (FTC) is the second most common differentiated thyroid cancer and accounts for approximately 10–15% of all thyroid cancers. It occurs more frequently in women, and usually presents in the fifth and sixth decades of life. It tends to invade blood vessels and metastasise by haematogenous spread to distant sites, most commonly to the bones and lungs. The incidence of distant metastasis in FTC has been reported as 6–20%.^{1–4} Survival in FTC cases is associated with older age at the time of diagnosis, larger tumour size, capsular invasion, male sex and presence of distant metastases.^{5,6} Long-term survival rates in patients with metastatic FTC range from 31% to 43%.^{7,8}

Distant metastasis may be the initial presentation of the disease or it may occur after initial treatment for cancer.⁷ The incidence of distant metastasis after total thyroidectomy for thyroid cancer is between 7% and 23%^{9–11} while for patients presenting initially with distant metastasis, it is approximately 1–9%.^{7,8,12} In the latter group, resection of

the thyroid is important to facilitate radioiodine ablation of the tumours.^{7,15} Few papers have been published on the management and outcomes of patients with FTC who already have distant metastasis at initial presentation versus those who develop metastases during clinical follow-up for FTC.^{7,8,14} The aim of our study was to compare the outcomes in these two groups of patients.

Methods

A retrospective cohort study was conducted of individuals diagnosed with FTC ($n=91$) referred between 2000 and 2013 to a tertiary referral centre. Of these, 20 patients were diagnosed with metastasis (either at first presentation or during the follow-up period) and were included in the final analysis. The study was approved by the institution's ethics board.

The demographic and pathological data collected from medical records were patient age, tumour site and size,

histology, thyroglobulin levels, imaging findings, treatment details and cause of death. Study outcomes included relapse free survival and overall survival.

Data were analysed with SPSS® version 21.0 (IBM, New York, US). Survival plots were constructed using the Kaplan–Meier method, and the Cox proportional hazards model was used to assess the relationship between prognostic factors and survival. Hazard ratios and their associated 95% confidence intervals were calculated. Data were compared with the chi-squared test. All reported *p*-values are two-tailed.

Results

The clinical, pathological and treatment characteristics of the two patient groups are summarised in Table 1. Of the 20 patients, 13 (65%) were women. The median follow-up duration was 5.5 years (range: 0.5–15 years). The median patient age at diagnosis was 65 years (range: 17–86 years). In 12 cases (60%), metastasis was the initial presentation. In the remaining 8 patients, metastasis developed at a median of 4.5 years after initial thyroid surgery (range: 2–8 years).

Metastasis at initial presentation

In patients where metastatic disease was diagnosed at initial presentation, the predominant sites were the bones (spine, pelvis, hip and scapula) (42%), followed by lungs (33%), brain (17%) and lymph nodes (8%). The diagnosis of metastasis in the bones and lungs was confirmed by biopsy, which showed widely invasive follicular carcinoma in all cases. In two cases, the metastasis was diagnosed by a craniotomy and dural resection of the tumour. All patients with pelvic and spinal involvement underwent

posterior stabilisation and fusion of the spine and fixation of the hip. Craniotomy and tumour resection was performed in two cases.

Following diagnosis of metastasis, 9 (75%) of the 12 patients underwent a total thyroidectomy. Three patients (25%) declined thyroid surgery and one of these chose to have no further treatment. All of the nine total thyroidectomy patients had adjuvant high dose radioiodine ablation. Two other patients also received radioactive iodine (RAI); the first was a lobectomy patient and the second patient did not have surgery. Of the eleven patients who received RAI, three underwent three further ablation procedures with a mean cumulative dose of 600–900mCi. One patient who had nodal metastasis and who underwent neck dissection along with total thyroidectomy developed further lung metastasis.

Thyroglobulin levels dropped from a mean of 9,405.9ng/ml (standard deviation [SD]: 1,766.7ng/ml) before treatment to 1,478.0ng/ml (SD: 2,016.0ng/ml) (*p*=0.33). Following treatment, thyroid stimulating hormone was suppressed in three patients (25%).

Five of the twelve patients in this group died (42%). Four of these (33%) died of advanced metastatic disease while one died from complications of acute myeloid leukaemia. Disease is stable in the remaining seven patients, who remain under surveillance.

Delayed metastasis

Delayed metastasis after initial thyroid surgery was seen in eight patients (40%). The median time to metastasis after initial treatment was 4.5 years (range: 2–8 years). The predominant site of metastasis was the lungs (50%), followed by bones (25%), regional lymph nodes (13%) and brain (12%). The initial surgery performed in this cohort consisted of total thyroidectomy in six cases (75%) and

Table 1 Demographics of the study population with metastatic follicular thyroid cancer

Parameter studied	Metastasis as initial presentation (<i>n</i> =12)	Delayed metastasis (<i>n</i> =8)	<i>p</i> -value
Mean age (SD)	68.5 (SD: 7.8)	56.5 (SD: 19.4)	>0.05
Female-to-male ratio	7:5	6:2	>0.05
Histology	12 WIFC	6 WIFC, 2 MIFC	>0.05
Surgery	9 total thyroidectomy, 1 lobectomy, 2 with no surgery	6 total thyroidectomy, 2 lobectomy	>0.05
Capsular invasion	8/10	7/8	>0.05
Lymphovascular invasion	5/10	7/8	>0.05
Extrathyroidal extension	1/10	3/8	>0.05
Adjuvant radioactive iodine	11/12	5/8	>0.05
External beam radiotherapy	5/12	3/8	>0.05
Chemotherapy	1/12	1/8	>0.05
Predominant site of metastasis	Osseous	Pulmonary	
SD = standard deviation; WIFC = widely invasive follicular carcinoma; MIFC = minimally invasive follicular carcinoma			

lobectomy in two cases (25%). The two patients who underwent lobectomy refused completion thyroidectomy or any other treatment. Initial histology showed widely invasive follicular carcinomas in six cases (75%) and minimally invasive carcinomas in two cases (25%).

Of the four patients with lung metastasis, one with progressive metastasis underwent a left lung lobectomy. Bony metastasis (involvement of the spine) was seen in three patients and all of them received 5–6 cycles of external beam radiotherapy (dosages of 300–400cGy). One patient with spinal cord compression needed posterior instrumentation, and another with cranial metastasis underwent a craniectomy and resection of an extradural tumour.

Before treatment for metastasis, the mean thyroglobulin level in this group was 325.5ng/ml (SD: 632.3ng/ml) compared with 297.6ng/ml (SD: 592.7ng/ml) thereafter. Following treatment, thyroid stimulating hormone was suppressed in four patients (50%). In the remaining four cases, levels dropped but not to within normal range.

The disease specific mortality rate in patients who developed metastasis following initial thyroid surgery was 50% (4/8). Two other patients died of illnesses not related to thyroid malignancy (myeloid leukaemia and myocardial infarction). Disease is stable in the remaining two patients, who remain under surveillance.

Comparison of the two groups

The overall mortality rate in the study population was 55% but the disease specific mortality rate was 40%. There were no statistically significant factors that predicted survival on univariate analysis (Table 1). There was no difference in survival for patients who were diagnosed with metastatic disease on initial presentation versus those who developed metastasis after initial treatment for FTC ($p=0.55$) (Fig 1).

Discussion

In this study, 12 patients were diagnosed with metastatic disease on initial presentation while 8 developed metastasis during the follow-up period after initial thyroid surgery. There was no difference in survival outcomes between the two groups. The mortality rate in the first cohort was 33% compared with 50% in the delayed metastasis group.

There is no consensus on the optimal management for patients who are diagnosed with metastasis on initial presentation for thyroid cancer. Sampson *et al* proposed that those presenting with metastatic disease should be managed aggressively with total thyroidectomy followed by RAI.¹⁴ The advantage of this strategy is that a large dose of ablative RAI can be given with no competition from the thyroid gland and it also avoids the potential problem of local recurrence.⁷

The literature on long-term survival with metastatic differentiated thyroid cancer is relatively scarce. Disease specific survival rates at five years have been reported as between 26% and 39% for patients with metastatic disease.^{8,15} In the present study, for those diagnosed with metastatic disease on initial presentation, osseous metastasis was

Figure 1 Kaplan-Meier survival plots for patients with metastatic disease on initial presentation (Mets at presentation) and those who developed metastasis during their follow-up period (Delayed mets)

the most common form whereas for those who developed metastasis during the follow-up period, it was mostly located in the lungs. The mortality rate for patients who presented with metastatic disease at the outset was 33%, which is similar to other studies.¹⁶

Although the difference was not statistically significant, the improved survival in our study for patients with osseous metastases versus pulmonary metastases is in contrast to the findings reported in the literature. Durante *et al* showed that those with osseous metastasis had a significantly poorer ten-year overall survival rate than those with pulmonary metastasis (25% vs 63%, $p<0.001$).¹⁷ Other studies have shown similar results.^{15,18,19} Poor outcome in osseous metastasis may be due to lack of effectiveness of RAI.¹⁹ Resecting the osseous metastasis where possible using an aggressive surgical approach may improve survival in cases with FTC.²⁰ In our study, all patients with osseous involvement underwent excision and stabilisation, which probably explains the improved survival.

A few studies have previously shown RAI avidity to be an independent prognostic factor for cancer specific survival.^{14,16,20} RAI-avid metastatic lesions are likely to be well differentiated and respond to RAI therapy. In the present study, 16 patients (80%) had RAI-avid lesions and underwent ablation. There was no statistical difference in survival for those who received RAI versus those who did not. This may be explained by the fact that our study only investigated FTC, unlike the previous studies, which also looked at other types of differentiated cancers.

Study limitations

The limitations of this study include its retrospective nature and small samples, which could lead to inherent

selection bias. Furthermore, the heterogeneity of treatment of a rare problem could add to the potential bias. The prognosis for FTC generally depends on age, site of metastasis, iodine avidity and pattern of presentation. However, none of the parameters studied were significant predictors of survival.

Conclusions

This study suggests there is no significant difference in short-term survival for patients with metastatic FTC on initial presentation versus those who develop metastases as a delayed event after their initial treatment for thyroid cancer. The clinical outcome and prognosis of patients with metastatic disease is poor compared with those who have no metastasis. Despite this, nearly half of the patients were alive at a median of five years following treatment, even in the presence of metastatic disease. Individuals who present with metastatic FTC should therefore be treated aggressively with thyroidectomy, radioiodine ablation and resection of the metastasis where possible.

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