

Pattern of regional metastases and prognostic factors in differentiated thyroid carcinoma

Metastatizzazione linfonodale e fattori prognostici nel carcinoma differenziato della tiroide

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SUMMARY

The meaning of nodal metastases in well-differentiated thyroid carcinoma is controversial. The Authors analyse the impact of lymphatic spread reviewing 1503 cases of well-differentiated thyroid carcinoma treated at the National Cancer Institute of Rome between 1988 and 2005, in order to detect significant prognostic factors through multivariate analysis. Overall, 462 cases of locally advanced well-differentiated thyroid carcinoma, were considered. A multivariate analysis of a subgroup, comprising 97 N+ consecutive cases of well-differentiated thyroid carcinoma, previously untreated, was performed to study prognostic factors for local (N+) and distant (M+) metastasis in well-differentiated thyroid carcinoma. Of the 97 cases, 88 were submitted to surgery for a large well-differentiated thyroid carcinoma, 9 for occult differentiated thyroid carcinoma. After surgery, 12 patients were lost to follow-up, 8 resulted pathologically negative, therefore only 77 cases of pN1 well-differentiated thyroid carcinoma were studied. Considering all cases of well-differentiated thyroid carcinoma, 10-year-overall survival was 58.7% for locally advanced well-differentiated thyroid carcinoma, compared to 94.8% in low stage cases. Neck dissection, margin infiltration and extra-capsular spread were significant prognostic factors. The Authors present a retrospective study of 77 patients with primary differentiated thyroid carcinoma, submitted to thyroidectomy and neck dissection aimed at analysing distribution of nodal metastases according to Robbins' levels classification and defining their prognostic value. All N1b cases, retrospectively reviewed (n. 77), presented clinical and histological evidence of neck nodes metastases from differentiated thyroid carcinoma; histological reports indicated tumour localisation and topographical distribution of metastases; papillary carcinoma was the most common type (72 cases), followed by follicular carcinoma (5 cases). Surgical treatment always comprised total thyroidectomy and 6th level dissection. Overall 52 cases were submitted to monolateral neck dissection, 25 to bilateral neck dissection. Treatment of the lateral neck was postero-lateral neck dissection (n. 53), selective lateral neck dissection (n. 20), modified radical and radical (n. 29). Cervical level IV was the most frequently involved (52%), extra-capsular spread of metastases was identified in 22% of the cases. Statistically significant prognostic factors for distant metastases and recurrence on the neck were follicular carcinoma ($p < 0.01$) and extra-capsular spread ($p < 0.001$). Age, pT, sex, number of positive nodal metastases, T-extension and the number of nodal positive levels were not significant. In the Authors' experience, histological grade of differentiation, wide tumour excision and neck dissection, in cases of N1b well-differentiated thyroid carcinoma, without residual disease (R1, R2), in the central and lateral neck, are determinant prognostic factors. Extracapsular spread in particular, was found to be a highly predictive factor either of distant metastasis or regional recurrence.

KEY WORDS: Thyroid carcinoma • Nodal metastases • Extra-capsular spread

RIASSUNTO

Il significato delle metastasi linfonodali nel carcinoma differenziato della tiroide è tuttora controverso. Gli Autori analizzano il valore prognostico della metastatizzazione linfonodale, mediante lo studio retrospettivo di 1503 casi di carcinoma differenziato della tiroide, trattati presso l'Istituto Nazionale Tumori "Regina Elena" di Roma, nel periodo compreso tra il 1988 ed il 2005. In particolare è stato estrapolato un sottogruppo di 77 casi di carcinomi sottoposti a tiroidectomia totale, svuotamento linfonodale ricorrentiale (6° livello) e svuotamento linfonodale laterocervicale per metastasi linfonodali (pN1). Quest'ultimo è consistito in uno svuotamento selettivo postero-laterale (livv. 2-5) in 53 casi, selettivo laterale (livv. 2-4) in 20 casi, radicale modificato o radicale in 29 casi. Il livello linfonodale maggiormente interessato è risultato essere il 4° (52%). La metastatizzazione linfonodale extracapsulare è stata documentata nel 22% dei casi. Sono stati analizzati mediante analisi multivariata i seguenti parametri: età, sesso, pT, istotipo, il numero di linfonodi, il/i livello/i cervicali coinvolti, secondo la classificazione di Robbins, la diffusione metastatica extra-capsulare dei linfonodi. Sono risultati statisticamente significativi per la metastatizzazione a distanza e la recidiva linfonodale la variante follicolare ($p < 0,01$) ed il coinvolgimento extracapsulare delle metastasi linfonodali ($p < 0,001$). Non sono per contro risultati significativi l'età, il sesso, il numero di linfonodi metastatici, le dimensioni di T. Nell'esperienza degli Autori l'extracapsularità linfonodale costituisce un importante parametro clinico predittivo del comportamento biologico di un carcinoma tiroideo differenziato e localmente avanzato. Un corretto approccio chirurgico del tumore primitivo e delle stazioni linfonodali cervicali laterali e del compartimento mediano è allo stato attuale determinante ai fini dell'esito oncologico della malattia.

PAROLE CHIAVE: Carcinoma tiroideo • Metastasi linfonodali • Metastasi extra-capsulari

Introduction

From an analysis of the literature, the value of nodal metastasis (N+) appears controversial: some reports consider them as having a good prognostic impact on survival, some relate them to higher rates of recurrences and survival decrease, while other Authors hold that the presence of N+ is valueless from a prognostic point of view.

Its incidence in differentiated thyroid carcinoma (DTC) is high, around 40-80% of the cases^{1,2} and it varies in relation to each histological variant: papillary carcinoma 80%, follicular and Hurtle cells carcinoma 10-15%³⁻⁵.

In the present investigation, 97 cases of DTC nodal metastases have been retrospectively examined, all homogeneously treated in the same Institution, by means of thyroidectomy and neck dissection. The rates of regional and distant recurrences were determined according to histopathological evaluation of pathological variants and nodal metastases were defined by levels, number, site and extracapsular spread (ECS)⁶.

Materials and Methods

A total of 1503 patients were treated for DTC at the National Cancer Institute of Rome "Regina Elena" between 1988 and 2005. A sub-group of 97 patients with nodal metastases in the lateral neck (N1b) was selected, who had undergone total thyroidectomy and neck dissection, unilateral or bilateral. Of these, 12 cases were excluded from the study due to lack of information and 8 due to the absence of nodal metastases at pathological examination. Finally, therefore, 77 cases of nodal lateral metastases for DTC were considered. The demographic characteristics of the series were as follows: 30 male and 47 female, aged between 18 and 77 years (mean 51).

According to the Shah risk group classification, this series was divided into two sub-groups: 33 patients ≤ 45 years old (43%) and 44 > 45 years old.

All patients were submitted to total thyroidectomy. Pathological findings showed 72 papillary carcinomas (93%) and 5 follicular carcinomas (7%).

Surgical treatment of the neck consisted of the 6th level and lateral neck dissection as reported below:

- selected neck dissection levels 2-5: 53 cases;
- selected neck dissection levels 2-4: 20 cases;
- modified radical/radical neck dissection levels 1-5: 29 cases.

Lateral neck dissection was ipsilateral to the tumour side in 52 cases and bilateral in 25, globally comprising overall 102 hemi-necks.

Nodal capsular infiltration and tumour extension were examined. In case of primary multifocal tumour, nodal metastases were considered ipsilateral in the event of its localization in the same side as the largest thyroid nodule.

All patients were submitted to post-operative ¹³¹I iodine ablation.

In the present series, clinical follow-up was performed in the same Institution, for a period ranging between 4 and 16 years (median 7 years).

Pathological staging was performed following surgery, according to the TNM (6th edn.)⁷. Nodal extra-capsular spread (ECS) was assessed in all the lymph nodes and cervical levels were studied and divided according to Robbins classification⁸.

Multivariate analysis of the prognostic factors, patient- and tumour-related, has been carried out.

Results

Papillary carcinoma was observed in 93% and follicular carcinoma in 7% of the cases; ipsilateral metastases were detected in 63 patients (82%) and bilateral metastases in 14 cases (18%). The pathological T-staging was: pT1 22%, pT2 31%, pT3 9% and pT4a 38%.

Nodal cervical metastases in the lateral neck were studied considering the number of N+, of involved levels, the evidence of nodal extra-capsular spread.

The mean number of metastatic nodes was 6.2 per patient (ranging between 1 and 43). The mean number of cervical levels involved was 2 (from 1 to 5) per patient. In the present series, 45% had more than 3 metastatic nodes and 22% had ECS in one or more lymph nodes. Examining the data collected from our series, the 4th level resulted as that most commonly involved (52%) (Table I), followed by the 3rd, the 6th, the 2nd, the 5th and finally the 1st level, with rates corresponding, respectively, to 45%, 43%, 38%, 8% and 4%.

As far as concerns the extension of the tumour inside the gland, in the subgroup of 63 cases with ipsilateral metastases, results showed:

- one neoplastic nodule in the thyroid in 65% of cases;
- more than one neoplastic nodule, in the same lobe, in 3% of cases.

Both thyroid lobes were involved in 31%.

A total of 8 out of 14 patients with bilateral metastases presented multiple neoplastic nodules in the thyroid.

With regard to the histology variant, patients with follicular carcinoma developed 69% of recurrences after 6 years, vs 18% with papillary carcinoma.

Considering cervical nodal involvement, bilateral metastases were detected in 29% of cases, when the tumour was located bilaterally in the gland, and in 13% of cases with a monolateral location. In only one case was the metastasis found contralaterally to the tumour.

At clinical follow-up, distant metastases (DM) were observed in 8/77 cases (10%) and nodal recurrences (NR) in 5/77 (6%).

As far as concerns the sub-group of 8 patients with DM, 5 had > 3 metastatic nodes and > 1 metastatic level involved (Table I).

ECS was found in 7 out of 8 cases with DM and in 3 out of 5 patients with NR.

Table I. Risk factors for regional and distant recurrence in the 77 patients.

Variable	No. patients	Neck recurrence (%)	Distant metastases (%)
Histology			
Papillary	72	4 (6)	6 (8)
Follicular	5	1 (20)	2 (40)
Age (yrs)			
≤ 45	33	2 (6)	5 (15)
> 45	44	3 (7)	3 (7)
Sex			
M	30	3 (10)	4 (13)
F	47	2 (4)	4 (9)
Tumour pT			
pT1	17		
pT2	24		2 (8)
pT3	7	1 (14)	2 (29)
pT4	29	4 (14)	4 (14)
Tumour site			
Unilateral	50	3 (6)	7 (14)
Bilateral	27	2 (7)	1 (4)
Lymph nodes pN			
pN1a	63	4 (6)	5 (8)
pN1b	14	1 (7)	3 (21)
No. positive nodes			
≤ 3	41	1 (2)	3 (7)
> 3	36	4 (11)	5 (14)
Extracapsularity			
No	60	2 (3)	1 (2)
Yes	17	3 (18)	7 (41)
No. Positive levels			
1	30	3 (10)	2 (7)
> 1	47	2 (4)	6 (13)
Total	77	5 (6)	8 (10)

Considering the group of distant metastases and nodal recurrences together, i.e., 13 patients, ECS was detected in 10 cases (77%).

On the other hand, considering the subgroups positive to ECS (17 cases) and negative to ECS (60 cases), in the former, there were 10 cases of recurrences (nodal or distant metastases) (59%), and, in the latter, only 3 cases with an incidence of 5%.

In order to determine the prognostic value of those factors, related to the tumour and to the patients, histology, age, sex, tumour extension, side of lymph node metastases, number of metastatic nodes and positive levels, ECS were statistically analysed

Multivariate analysis of these data, focused on the risk of NR and DM, in accordance with the Cox regression model¹⁹, revealed as significant adverse prognostic factors: the follicular variant ($p < 0.01$) and the nodal extra-capsular spread ($p < 0.001$).

Discussion

The prevalence of DTC in females was confirmed in the present study⁹⁻¹¹ and the median age (51 years) was comparable to that reported in other larger series^{10,12}.

According to these data and considering the large number of cases with only one metastatic neck level, in the present series a fairly homogeneous uniformity in the distribution of nodal metastases has been demonstrated in all cervical levels except the 1st and 5th^{13,14}. It probably means that there is no progressive metastatic spread from the thyroid to the cervical lymph nodes but that metastases do not follow a regular path, skipping to different cervical levels. At multivariate analysis, significant prognostic factors were shown to be the follicular histology variant ($p < 0.01$)^{3,12,15} and, above all, ECS ($p < 0.001$). No reference to this peculiar prognostic factor has been found in the literature, not even by those Authors, who reported the negative impact, on prognosis, of nodal metastases^{11,16-19}.

Conclusions

Patients with thyroid cancer are usually stratified into low, intermediate and high risk categories on the basis of prognostic factors which are related to the patient, to the tumour and to the treatment^{9,20,21}.

Age, sex, size, nodal extra-capsular invasion and metastases are well-defined prognostic factors^{12,22}.

The prognostic significance of nodal involvement is still

debated in the literature; as in most retrospective analyses, it is evaluated in the whole population, that includes all thyroid tumours of any risk category. The statistical weight of nodal involvement is consequently reduced due to the dispersion arising from the included low and intermediate risk cases, which represent 80% of the entire thyroid cancer population²³⁻²⁵.

In the present study, which examined the advanced cases only, the prognostic impact of nodal metastases resulted highly significant.

From our study, nodal extra-capsular spread was found to be a highly predictive prognostic factor either of distant metastasis or loco-regional recurrence.

In the literature, nodal metastasis is not considered as such an important prognostic factor^{1 9 10 26 27} and its treatment

still represents a major controversial issue. One of the most adopted techniques in the past was “node picking” or “berry picking”²⁸. This “limited” approach to nodal metastases appears to have the advantage of low morbidity and simplicity but it is accompanied by a high rate of residual nodal disease. All the cases in the present series were submitted to selected or modified radical neck dissection. This, in the Authors’ opinion, is the only way to achieve radical excision preserving the anatomy and the function of the neck.

The correct surgical treatment of the primary thyroid tumour and the cervical nodes of the central and lateral neck represents, at the present time, the standard option in the treatment of thyroid carcinoma, together with ¹³¹I ablation and TSH-suppression treatment.

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