Revisiting the Evidence for Routine Transcervical Thymectomy for the Prevention of Thymic Carcinoid Tumours in MEN-1 Patients

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Keywords
Thymus · Carcinoid · Parathyroidectomy · Multiple endocrine neoplasia type 1

Abstract

Background: Malignant thymic carcinoids are uncommon tumours among patients with multiple endocrine neoplasia type 1 (MEN-1). Current guidelines advise performance of a preventative, routine transcervical thymectomy (TCT) during parathyroidectomy, although data on the yield is scarce. In this review, we aimed to revisit available literature to investigate and summarize the efficacy of routine TCT for the prevention of thymic carcinoid tumours among MEN-1 patients after searching four databases (PubMed, Embase, Medline, and Cochrane Library).

Summary: Seven eligible studies were identified: retrospective observational studies: 3 and case reports describing one or more patients: 4. A total of 122 patients were included, 56 males (45.9%) and a pooled mean age of 40 years (±10). All underwent a routine TCT as part of parathyroidectomy; no details on the extent of TCT were available. Overall, only one (0.9%) incidental carcinoid was found. However, although all other patients underwent prophylactic TCT at the time of parathyroidectomy, an additional nine (7.4%) developed a thymic carcinoid during follow-up, after a median time of 36 months (range: 8–226).

Key Messages: There is currently not enough evidence to support the efficacy of a routine TCT to prevent the development of thymic carcinoid among MEN-1 patients. As this is a rare but potentially highly aggressive tumour, attention should be shifted towards improving follow-up programs and developing specific imaging-screening protocols. This enables early detection of thymic carcinoids in a timely manner and improves outcomes, even after performance of a routine TCT.

Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is an autosomal dominant familial cancer syndrome with a prevalence ranging from 1:10,000 to 1:100,000. The tumour suppressor gene MEN-1 on chromosome 11q13 and its protein-product menin were identified in 1997 [1]. Apart from anterior pituitary, parathyroid, and pancreatic endocrine tumours, other rarer tumours have also been noted to develop in carriers of this gene. Specifically, an association between the occurrence of highly aggressive thymic carcinoid tumours in MEN-1 has been described [2, 3].

Approximately 150 cases of thymic carcinoid have been reported since 1972, in the literature, underlining the rare nature of this tumour [2, 4]. Of these, about a quarter were in patients with MEN-1 and overall, thymic carcinoids are described in approximately 3% of patients with MEN-1 [4]. Proposed adverse characteristics for de-
Developing this disease are male sex, age over 40, and a history of tobacco smoking [5, 6]. However, considering their aggressive behaviour and the absence of true robust risk factors, discussing the value of prophylactic thymectomy and surveillance is very relevant.

Transcervical thymectomy (TCT) has often been performed simultaneously with neck exploration in MEN-1 patients at initial parathyroidectomy [7, 8], with an aim to remove any ectopic or missing parathyroid tissues within the thymus. Although data on the yield for TCT to identify additional parathyroid glands is scarce [8, 9], there is an even greater paucity of data regarding the need for routine TCT for the prevention of thymic carcinoids in MEN-1 patients. Given the uncertainty surrounding this issue, we performed a review to investigate and summarize the efficacy of TCT for the prevention of thymic carcinoid tumours among MEN-1 patients undergoing neck exploration for parathyroidectomy.

### Methods and Results

A case series was built after review of available literature for observational studies or case reports on routine prophylactic TCT for MEN-1 and the occurrence or development of thymic carcinoids. This case series was set up in compliance with the PROCESS Guidelines [10]. Four databases (PubMed, Embase, Medline, and Cochrane Library) were queried from inception until July 10, 2021 using the following free text search strategy:

**Table 1. Baseline characteristics of the seven studies included in the review**

| Author                  | Year | Country   | Study design           | Patients, n | Male, % | Mean age, years |
|-------------------------|------|-----------|------------------------|-------------|---------|-----------------|
| Burgess et al. [13]     | 2001 | Australia | Case report            | 1           | 100     | 30              |
| Lim et al. [11]         | 2006 | Singapore | Case report            | 2           | 50      | 49              |
| Tonelli et al. [16]     | 2006 | Italy     | Retrospective cohort study | 45         | 36      | 40              |
| Powell et al. [9]       | 2008 | US        | Retrospective cohort study | 66         | 47      | 34              |
| Goudet et al. [12]      | 2009 | France    | Retrospective cohort study | 6           | 83      | 49              |
| Khoo et al. [19]        | 2012 | Singapore | Case report            | 1           | 100     | 29              |
| Sadacharan et al. [14]  | 2013 | India     | Case report            | 1           | 100     | 56              |

**Fig. 1.** Flowchart depicting the search and included and excluded records.
Table 2. Demographic, clinical, and operative characteristics of all patients included

| Variable                                      | n (%)     | (n = 122) |
|-----------------------------------------------|-----------|-----------|
| Patient and operative characteristics         |           |           |
| Sex (male)                                    | 56 (45.9) |           |
| Age (mean [SD]), years                        | 40 [±10]  |           |
| Prophylactic intervention performed           |           |           |
| Total parathyroidectomy + TCT                 | 51 (41.8) |           |
| Subtotal parathyroidectomy + TCT              | 3 (2.5)   |           |
| Unspecified extent of parathyroidectomy + TCT | 68 (55.7) |           |
| Outcome variables                             |           |           |
| Incidental thymic carcinoid found during TCT  | 1 (0.8)   |           |
| Thymic carcinoid diagnosed during follow-up   | 9 (7.4)   |           |

(“Multiple endocrine neoplasia type 1” OR “MEN-1”) AND ("thymic carcinoid") OR ("thymic neuroendocrine") AND ("prophylactic" OR "routine" OR "incidental") AND ("thymectomy"). All bibliographies of included articles and relevant reviews were manually searched for additional work. Two authors (MdJ and RP) selected potentially eligible studies, initially based on title and abstract, and later by full-text articles. We accepted randomized controlled trials or observational studies that included patients of any age who underwent a routine TCT in the setting for MEN-1, published as full-length articles in peer-reviewed journals, which mentioned data on thymic carcinoid tumours. We excluded reviews, letters, conference proceedings, and non-English publications. One author (MdJ) extracted the following data from each article into a standardized extraction spreadsheet template: first author, year published, study design, country, sample size, percentage male, mean age, intervention, outcomes, and key findings.

From the 35 records identified in our systematic search, we removed 20 duplicates, excluded eight articles based on title and abstract, further excluded three articles because of use of non-English language. The manual search of the bibliographies of included articles revealed another three records. Thus, in total, seven articles were included in the review, as shown in Figure 1. Of the seven included studies (Table 1), three were retrospective observational studies and the remaining four were case reports describing one or more patients. No randomized control trials or prospective studies were found. Two studies were set in Europe, one in America, one in Australia and three in Asia. The total cohort of patients over the seven studies combined was 122 (Table 2), with about half of patients being male (45.9%). No details of the exact extent of the TCT were provided.

Overall, only one case (0.9%) of incidental carcinoid was found during routine TCT performed simultaneously with parathyroidectomy [11]. This case concerned a female MEN-1 carrier who underwent a prophylactic TCT during parathyroidectomy for primary hyperparathyroidism with multiglandular disease at age 43. While the authors state that preoperative imaging did not reveal any mediastinal mass, histology of the removed thymus did reveal a moderately differentiated thymic carcinoid. No further details of size or histology were unfortunately provided. However, although all other patients underwent prophylactic TCT at the time of parathyroidectomy, an additional 9 patients (7.4%) developed a thymic carcinoid during follow-up [11–14]. Median overall time to development of a thymic carcinoid was 36 months (range: 8–226) for all cases identified. The mode of detection was with computed tomographic (CT-) scan of the thorax for 3 patients [11, 13, 14]. Of only 3 patients, any longer-term data was described [13, 14]. Overall, none of these were reported to have developed recurrent or metastatic disease during the follow-up period described, which ranged from 6 months to 4 years.

Discussion

Thymic carcinoids are very rare tumours, with only approximately 150 cases described in literature, and are found to be associated with the MEN-1 gene mutation [2, 3, 15]. Although the survival of patients with this mutation was traditionally mostly predicted by the development of potentially malignant gastroenteropancreatic neuroendocrine tumours, recent developments in multimodality treatments have improved outcomes for this tumour [4, 16]. Therefore, the occurrence of other, rarer but potentially more aggressive tumours such as thymic carcinoids, might have become more significant in determining the survival of MEN-1 patients [17].

Thymic carcinoids are considered highly biologically aggressive, depending on histology and local invasion. Therefore, current consensus guidelines for the diagnosis and therapy of MEN-1 patients [17, 18] state that the preferred parathyroid operation includes the performance of a simultaneous transcervical, near-total thymectomy. However, no reference to evidence is made to corroborate this statement. In our search of available literature, only one case of incidentally found thymic carcinoid in a routine TCT-specimen for a MEN-1 patient was identified.
Conversely, an additional 9 patients were identified who had developed a thymic carcinoid during follow-up, after they had undergone a prophylactic TCT [11–14], possibly because performing a TCT will only remove about half of all thymic tissue. These findings seem to indicate that TCT does not reliably provide prophylaxis against thymic carcinoid.

It could thus be more reasonable to focus on strategies for early detection of these tumours rather than preventing them from occurring by performance of a routine TCT. Unfortunately, several series have reported on the lack of reliable hormonal or biochemical abnormalities to aid in diagnosing this tumour [2, 3, 12]. Moreover, on more detailed molecular screening, Goudet et al. [12] could not identify a specific subgroup of mutations within the MEN-1 gene that was able to predict the development of a thymic carcinoid. Conversely, since Teh et al. [5] noted an increased incidence of this tumour amongst those with a family member who had previously developed a thymic carcinoid, there might be a yet unknown genotype-phenotype correlation.

Due to the current inability to reliably predict the development of a thymic carcinoid, these patients should be subjected to radiological or functional imaging follow-up protocols, to diagnosis the condition at an early stage, and to increase the chances of a favourable outcome. Using octreotide scintigraphy, a pooled analysis by Goudet et al. [12] including three series, reported a sensitivity of 89% for this modality, although others have reported negative octreotide scans [2, 3]. For all patients in whom a thymic carcinoid developed after TCT included in our review, this tumour was diagnosed on CT-scan of the chest, thus suggesting a role for regular screening with this technique for either all or selected MEN-1 patients, i.e., those with family members who had developed a thymic carcinoid. As a possible alternate imaging modality without concerns surrounding the radiation dose associated with yearly CT-scan, MRI-scan could be considered while positive, yet limited data regarding the sensitivity of this modality are available [2, 12].

Our review has several limitations, in that the data available on thymic carcinoids in general is very limited and specifically among MEN-1 carriers. Moreover, of those cases described, there could be a publication bias, focussing more on patients who, at some point, did develop this type of tumour. Thus, the overall incidence could be even lower. On the other hand, there could be potential differences in techniques or completeness of the TCT or of histologically accurate diagnosis, influencing the number of cases published.

Our data should be viewed in the light of these potential shortcomings, and conclusions should thus be drawn with caution.

**Conclusion**

In conclusion, there is currently not enough available evidence to support the performance of a routine TCT during parathyroidectomy for MEN-1 carriers to prevent the development of thymic carcinoids. Since there could be additional reasons for simultaneously performing a TCT in terms of removing parathyroid tissue, the benefits of this procedure might outweigh the risks for that indication only. Specifically, for those MEN-1 mutation carriers with a positive family history for thymic carcinoid, there is place for routine follow-up programs, as currently in place. Focus should therefore be shifted towards improving available tools and specific imaging-screening protocols to detect the development of this rare but potentially deadly tumour in a timely manner to further improve outcomes, even after performance of a routine TCT.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

The authors have no funding source to declare.

**Author Contributions**

Mechteld de Jong: substantial contributions to the acquisition, analysis, and interpretation of data for the work; drafting the work; and final approval of the version to be published. Rajeev Parameswaran: substantial contributions to the conception or design of the work; revising it critically for important intellectual content; and final approval of the version to be published.

**Data Availability Statement**

Data are available on request.
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