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Review article

Conservative or radical surgery for pediatric papillary thyroid carcinoma: A systematic review of the literature

Xi Jin [a,1], Liam Masterson [a,1,*], Anant Patel [a], Liz Hook [b], James Nicholson [c], Sarah Jefferies [d], Mark Gaze [e], Ramez Nassif [f], Robert Eller [g], Tony Hulse [h], Piyush Jani [a]

[a] Department of Otolaryngology, Head and Neck Surgery, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
[b] Department of Pathology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
[c] Department of Pediatric Oncology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
[d] Department of Clinical Oncology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
[e] Department of Oncology, University College Hospital, London NW1 2PG, UK
[f] Department of Head & Neck Oncology, Norfolk & Norwich University Hospital, Norwich NR4 7UY, UK
[g] US Air Force and Army Voice Center, San Antonio, TX, USA
[h] Department of Paediatric Endocrinology, Guy's & St Thomas' Hospital, London SE1 7UH, UK

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ABSTRACT

Background: Pediatric papillary thyroid carcinoma (PTC) is characterized by an aggressive clinical course. Early diagnosis is a challenge and treatment consists principally of partial or total thyroidectomy ± neck dissection and radioactive iodine therapy. Due to the rarity of PTC in children, there is no consensus on optimal surgical treatment.

Methods and results: A literature search was carried out using PubMed, Embase, Medline, Cochrane and Web of Science. Seven studies (489 patients) investigating the outcome of surgically managed pediatric PTC were identified. No clear advantage in survival or recurrence rate was found for total thyroidectomy compared to other surgical approaches.

Conclusion: Despite the aggressive behavior of PTC, prognosis is good, with low mortality. After removal of disease and prevention of recurrence, reduction of iatrogenic complications are a priority in this age group. Due to the paucity of available evidence, this review cannot recommend conservative or radical surgery for pediatric papillary thyroid carcinoma. To answer this question, we recommend the establishment of a randomized controlled trial with adequately matched baseline variables.

Contents

1. Introduction

Papillary thyroid carcinoma (PTC) is a rare childhood cancer, accounting for 0.5–3% of all pediatric malignancies [1–3].

Pediatric PTC follows an aggressive course with frequent metastases to the regional lymph nodes and distant organs—most commonly the lungs. Early diagnosis is a challenge and a significant number of children present with metastatic disease. Recent research has shed light on various genetic abnormalities associated with PTC, in particular, mutations in the MAPK pathway involving RET/PTC and BRAF. A possible link with familial adenomatous polyposis (FAP) has also been suggested [4].

* Corresponding author. Tel.: +44 1223217578; fax: +44 1223217559.
E-mail address: lmm398@doctors.org.uk (L. Masterson).
[1] Equal contribution.

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Despite the frequency of metastatic disease at presentation, prognosis is generally very good [5]. Ten-year survival rates of >98% are reported [6]. However, there is no consensus on the initial surgical treatment for PTC in children. No randomized trials or even prospective studies have ever been performed in the pediatric population, and management has been extrapolated from adult practice and evidence, supported by data from retrospective case series in children. A radical approach to PTC with total thyroidectomy as the primary surgery has been advocated [7]. Whilst the rationale behind this method was to minimize the high recurrence rate of this tumor, extensive ablative surgery carries with it the inherent risks of permanent complications, such as hypoparathyroidism and recurrent laryngeal nerve palsy, which are particularly important in children as their growth and development may be affected. A more conservative strategy with less extensive surgery for early stage PTC, has been advocated by Enomoto et al. [8]. Although this latter study may not be adequately powered to unequivocally demonstrate this outcome, it may sow the seed of doubt regards a traditional total thyroidectomy approach for all cases.

To our knowledge, there have been no reviews of the literature looking into the optimal surgical approach for pediatric PTC. In this article we evaluate treatment options for this condition.

2. Methods

A comprehensive literature search was carried out using Pubmed, Embase, Medline, The Cochrane Library and Web of Science using the terms 'pediatric papillary thyroid carcinoma' and 'papillary thyroid carcinoma AND child*'. Articles were initially screened on the basis of title and abstract. Full texts of potentially eligible articles were then accessed for further evaluation and selection. References of the selected articles were reviewed to include any studies not revealed by the initial search (Fig. 1). Only articles published within the last 10 years were included to take into account advances in pediatric ENT surgical techniques.

Relevant data included age at diagnosis, sex, extent of disease at presentation, initial surgical treatment, permanent post-operative complications, post-surgical treatment, duration of follow-up and outcome.

3. Results

A total of 7 retrospective case series (489 patients) were identified that investigated outcomes of pediatric PTC treated with surgery (Table 1) [8–14]. The mean age of children at diagnosis ranged from 10 to 16 years and mean duration of follow-up ranged from 5.4 to 28.7 years. Locoregional (52%) and distant spread (~6%; pulmonary metastasis being the most common) were common features at presentation. Despite this, the survival rate was high, with 100% survival at 5 years and more than 98% of children surviving at 10 years. A statistical analysis comparing mortality for either surgical approach (partial versus total) was not possible to achieve due to the infrequent nature of this outcome.

4. Discussion

Pediatric thyroid cancer has an increasing incidence that may be due to a variety of factors e.g. environmental radiation exposure, genetic predisposition or improved diagnostics. Approximately 80% of cases are papillary thyroid carcinoma (PTC) [15].

The WHO recognizes 15 variants of PTC and this has importance with regards prognosis. In adults, columnar and tall cell variants are known to be associated with a more aggressive clinical behavior. In contrast, the follicular variant of PTC follows a more indolent course [15]. In pediatric cases, the diffuse sclerosing variant is relatively more common [16]. This important subtype is associated with a higher likelihood of locoregional and distant metastasis [17] and has a poorer overall prognosis [18,19].

Papillary carcinomas may display a RET/PTC rearrangement, BRAF or RAS mutation, all of which affect the mitogen activated protein kinase (MAPK) pathway. Pediatric cases of papillary thyroid carcinoma exhibit RET mutations and RET/PTC rearrangements more frequently than adults [20–22].

The RET proto-oncogene is a receptor tyrosine kinase molecule located on chromosome 10 that influences an intra-cellular signaling pathway commonly associated with papillary thyroid cancer. RET/PTC rearrangements have been demonstrated in up to 70% of pediatric thyroid cancer patients [23].

BRAF belongs to the family of RAF proteins that is activated by RAS binding, resulting in activation of the MAPK signal pathway by phosphorylation. BRAF mutations are less common in pediatric PTC, but become more frequent with age. This may be one factor contributing to the observation that prognosis becomes poorer with increasing age [22].

Further research into molecular markers of thyroid carcinoma in adults has led to earlier diagnosis for some cases e.g. the positive predictive value of needle biopsy in cases exhibiting equivocal cytology may be improved by testing for BRAF, RAS or RET/PTC genetic sequence alterations. The significance of these findings in a

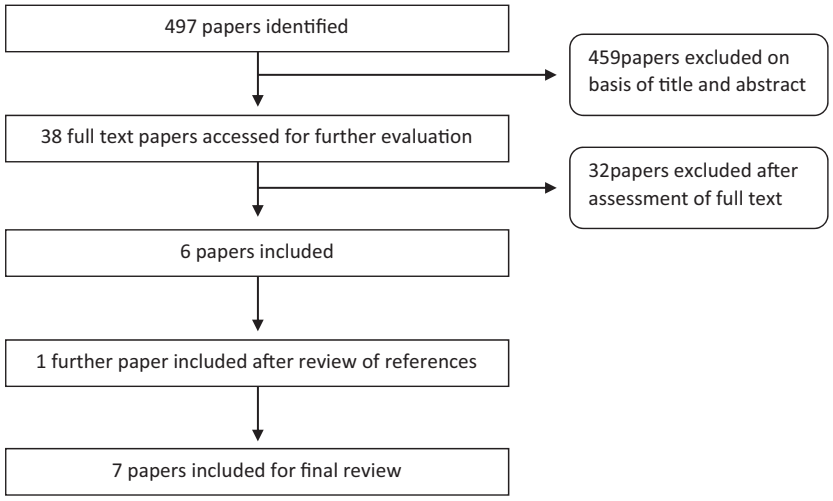

Fig. 1. Study flowchart.