Radiotherapy and Oncology 136 (2019) 113–120

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

The role of external beam radiotherapy in the management of medullary carcinoma of the thyroid: A systematic review

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ARTICLE INFO

Article history:
Received 25 October 2018
Received in revised form 9 March 2019
Accepted 29 March 2019
Available online 17 April 2019

Keywords:
Thyroid cancer
Medullary carcinoma
Radiotherapy
Systematic review

ABSTRACT

Objective: In order to clarify the role of external beam radiotherapy in the management of medullary thyroid cancer (MTC), a systematic review was undertaken.
Patients and interventions: Patients with MTC of any stage receiving radiotherapy, either as adjuvant postoperative treatment or as primary treatment for unresectable disease.
Design: Electronic searching Medline and ProQuest databases for randomised or non-randomised studies. A risk of bias assessment (ROBINS-I) was carried out for each study.
Main outcome measures: Overall survival, rates of locoregional recurrence, locoregional relapse-free survival.
Results: There were no randomised studies. Twenty-seven non-randomised studies were identified. Within four cohort studies, radiotherapy had no significant effect on overall survival. Within one prospective and 22 retrospective studies (of approximately 1200 patients), radiotherapy similarly had no consistent effect on overall survival but there was evidence that radiotherapy reduces the risk of locoregional relapse, particularly in those with nodal involvement, extrathyroidal extension or residual disease. In a meta-analysis of patients within four studies, radiotherapy reduced the risk of locoregional relapse by at least 38%. Evidence supports the use of doses of 60 Gy or greater and an interval between surgery and radiotherapy of less than two months. Thirteen of 63 patients (21%) treated for unresectable disease achieved a complete response. Acute morbidity was observed in relation to difficulty swallowing, xerostomia and skin reactions. Late morbidity was infrequent with a low incidence of xerostomia.
Conclusions: Radiotherapy should be considered for those at high risk of locoregional relapse, in particular those with nodal involvement, extrathyroidal extension or residual disease (microscopic or macroscopic).
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Medullary thyroid cancer (MTC) accounts for less than 5% of all thyroid cancers [1–3]. Up to 25% of cases arise in those with a family history of MTC, though this proportion varies between populations. Overall, the median age at diagnosis is slightly younger for familial cases (which can affect children) compared to sporadic cases, and familial cases tend to present with earlier stage disease and a higher frequency of multifocal or bilateral disease [4]. Prognosis is similar for both groups when corrected for age and stage [5,6]. Compared to other types of thyroid cancer, MTC tends to present with more advanced disease, with 30% of primary tumours demonstrating extracapsular extension, 70% presenting with lymph node metastases and 10% with distant metastases [7]. Distant metastases are more commonly seen or develop in those with lymph node metastases, and lymph node metastases are more commonly seen in those with extrathyroidal extension. In general, prognosis depends on stage at diagnosis [8–11] and on age at diagnosis [6,10,12,13]. The effect of age on prognosis appears greater in MTC than in other types of thyroid cancer [14]. A greater degree of advanced disease is seen in older patients and in men [10].

Optimal management includes total thyroidectomy and central compartment (level 6) clearance together with unilateral or bilateral neck dissection for those with evidence of or at high risk of nodal involvement [2,3]. A common theme is that more complete surgery is associated with better outcomes, although is not always clear whether less than complete surgery is due to failure to follow protocols or due to advanced disease which is unresectable despite a high level of surgical skill. Despite best intentions and skilled management, a complete (R0) resection is not always possible and a number will have microscopic (R1) or macroscopic residual disease (R2). There is therefore a need to consider whether other

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https://doi.org/10.1016/j.radonc.2019.03.033
0167-8140/

forms of treatment in addition to surgery (such as external beam radiotherapy) might increase the rate of locoregional control. Typically, rates of progression are slow, with a mean annual rate of increase in serum calcitonin of 117% [15]. Those with distant metastases at diagnosis have a 10-year survival of 40% [10] and a large proportion of those without distant metastasis at diagnosis develop distant metastasis over 5–20 years [11,16]. Locoregional recurrence may also develop over this time and contribute to local symptoms. Recurrent neck masses may not always be amenable to surgery and can compromise the airway and swallowing function. The question is whether postoperative radiotherapy might contribute to a lower risk of locoregional recurrence and (provided there are no significant long-term side effects from treatment) result in an otherwise better quality of life. Over the years, the role of radiotherapy has been controversial and only in the most recent updates of national guidelines [2,3], has radiotherapy been recommended as an option for those with residual disease after surgery or a high risk of local recurrence.

Radiotherapy techniques have changed considerably over the years so that, generally speaking, tumour doses are now higher and doses to normal tissues lower than 20–30 years ago. Because of the rarity of MTC, a number of case series go back as far as the 1940s when lower doses of orthovoltage or supervoltage radiotherapy were used with little sparing of normal tissues. By modern standards, such techniques would be regarded as having low effectiveness and high toxicity, with limited relevance to practice today. A much quoted early study of radiotherapy in MTC showed worse survival in those receiving radiotherapy [5]. This study highlights the difficulty in interpreting non-randomised studies where the treatment groups are far from balanced. In most studies, inevitably, patients receiving radiotherapy were of more advanced stage and considered to be at higher risk of relapse compared to those who did not receive it, by virtue of greater degrees of local invasion or nodal involvement. This confounding by disease severity is a major source of bias in this situation.

The purpose of this systematic review is to assess the effectiveness of radiotherapy either in the postoperative setting or when given for unresectable disease.

Methods

A protocol for this review was registered with PROSPERO [17] prior to the commencement of the review and the review carried out in line with the PRISMA statement [18].

Criteria for considering studies for this review

Types of studies, participants and interventions

Randomised or non-randomised studies of men or women with medullary thyroid carcinoma (familial or sporadic) of any stage receiving external beam megavoltage radiotherapy, either postoperatively or as primary treatment for unresectable disease.

Outcome measures

Incidence of local, locoregional or distant metastasis; overall survival and locoregional relapse-free survival at five and ten years; effects of radiotherapy on serum calcitonin; acute and late radiotherapy-related morbidity.

Search strategy for identification of studies

Electronic searches of Medline and ProQuest databases were carried out in March 2018 (and updated in October 2018) with identification of further studies from references cited in the papers identified by electronic searching. The search strategy is shown in Appendix A. There was no restriction by date of publication, language or duration of follow-up. Reports containing five or fewer cases or concerned solely with patients under the age of 18 were excluded. Duplicate reports were excluded. Reports with overlapping time-periods were considered if they contained unique information.

Risk of bias (quality) assessment

Formal risk of bias assessment was undertaken for each study using the ROBINS-I assessment tool [19]. This assesses risk of bias in six domains (patient selection, treatment allocation, measurement of outcomes, reporting of results, missing data and risk of bias due to confounding).

Data extraction and analysis

Data were extracted from each paper and summarised. Where possible data from patients under the age of 18 were removed. Studies with five or fewer patients receiving radiotherapy for MTC were excluded. Studies were separated into cohort studies and prospective/retrospective studies and effects on overall and locoregional progression-free survival reported qualitatively. A meta-analysis (not specified in the original protocol) using RevMan 5.3 software and a fixed-effects model (Nordic Cochrane Centre, Cochrane Collaboration 2014) was carried to estimate the extent to which radiotherapy might reduce the risk of locoregional recurrence.

Data relating to acute and late morbidity were collated and reported qualitatively.

Results

No randomised studies were identified. After exclusion of duplicate reports, 27 non-randomised studies met the inclusion criteria. There were four cohort studies, one prospective study and 22 retrospective series. The PRISMA flow diagram (Appendix B) details the number of records screened and the reasons for exclusion.

Risk of bias assessment

There was a low risk of bias in all domains except bias due to confounding (Appendix C). For studies where only a proportion of patients received radiotherapy, there was a lack of clarity as to the precise reasons for giving radiotherapy. These studies did not include an appropriate method of analysis to control for confounding variables (particularly primary tumour extent and degree of nodal involvement) such that these studies were judged to be at critical risk of bias. Though not explicitly stated, it is considered possible, or even likely, that patients receiving radiotherapy had more advanced stage than those not receiving radiotherapy and were therefore at greater risk of locoregional and distant metastasis. Studies where all patients received radiotherapy were considered to be at low risk of bias. However, reasons for recommending radiotherapy in these studies could not be determined.

Cohort studies

The four cohort studies were based on data from two cancer registries (Table 1). Three of these, from the Surveillance, Epidemiology and End Results (SEER) registry covering 26% of the US population, were from overlapping time-periods where the focus of each individual study was different. The longest time-period was covered in a study where the objective was to assess concordance with the American Thyroid Association (ATA) guidelines [20]. Non-concordance (less than a total thyroidectomy, for example) was associated with a worse outcome. Only 12% of 2033 patients

Table 1
Radiotherapy in medullary thyroid cancer: cohort studies.

Study	Study group	Years studied	Number of patients	Regional spread (%)[a]	Distant metastases (%)	Number with total thyroidectomy (%)	Number undergoing radiotherapy (%)
Rocky Mountain [14]	All patients	1973–1983	200	54	11	Not stated	Not stated
SEER [20]	All patients	1973–2006	2033	33	14	1606 (79%)	244 (12.0)
SEER [10]	All patients	1973–2002	(1252)	35	13	Not stated	148 (11.8)
SEER [21]	Selected patients[b]	1988–2004	(534)	59–66[c]	0	534 (100%)	66 (12.4)

[a] Regional spread defined as extrathyroidal extension, lymph node involvement or both.
[b] Selected patients were those without distant metastases who had undergone total thyroidectomy and had had at least one lymph node sampled.
[c] 59% had lymph node involvement and 66% extrathyroidal extension.

received radiotherapy (6% following a complete resection and 33% following an incomplete resection). For the whole group, cause-specific survival was 86% at five years and 80% at ten years. There was a higher proportion of non-concordance for surgery in the group not receiving radiotherapy. In the subset from a slightly shorter time-period [10], multivariate analysis identified radiotherapy (as well as age and stage at diagnosis) as being associated with a worse overall survival (hazard ratio 1.65; $P = 0.01$). The third cohort study [21] was restricted to 534 patients without metastatic disease who had undergone total thyroidectomy and sampling of at least one lymph node. Although in univariate analysis radiotherapy was associated with improved survival in 314 node-positive patients, this was not confirmed in multivariate analysis where radiotherapy had no significant effect on overall survival either in the whole group (HR 1.35; 95% confidence interval 0.57–3.37) or in group with positive nodes (HR 1.31; 95% c.i. 0.52–3.25). Levels of nodal involvement within the radiotherapy and no radiotherapy groups were not reported. Age, tumour size and nodal involvement were significant factors for overall survival in multivariate analysis. An older fourth study from the Rocky Mountain Cancer Data System covering all patients in 12 US states identified 200 patients with MTC over a 10-year period [14]. Five-year survival was 77% with surgery plus radiotherapy versus 83% with surgery alone. In 45 patients with regional disease (defined as extrathyroidal extension, nodal involvement or both), 5-year survival was 97% with radiotherapy and 62% without (P value not given).

Radiotherapy as post-operative treatment

The single prospective study was of intensity modulated radiotherapy (IMRT) in advanced thyroid cancer with just seven patients with MTC [22]. Because of the small numbers, the results of this study have been analysed together with the results from the 22 retrospective series. Within these 23 studies, there were eight studies from three centres, and within six of these studies the patient populations were either the same or overlapped. All six studies have been included where each study provided unique data but excluded from analysis where this would cause data duplication. Within the 23 studies (ignoring the duplication of approximately 150 patients), there were 1320 patients with MTC (531 men, 550 women, remainder unknown) of median or mean age 48.5 years (range 2–88) (Table 2). Where possible, data relating to those under the age of 18 were excluded. Eight studies included individuals under the age of 18; of these, three included children under the age of 10. Where data were provided, there were 863 sporadic cases and 203 familial (19%). Six studies excluded those with distant metastases. In a further 12 studies, distant metastases were present in 5–54% of patients at diagnosis (median 13%).

Total thyroidectomy had been performed in 717/1018 (70%) and unilateral or bilateral neck dissection in 433/816 (53%) (Table 2). Postoperative resection status was reported in nine studies: there were 167/411 (41%) complete (R0) resections, 105/336 (31%) resections with microscopic residual disease (R1) and 94/336 (28%) where there was macroscopic residual disease (R2).

Postoperative radiotherapy was given to 665/1320 (50%) and primary radiotherapy to 33 patients (2.5%). Radiotherapy was stated as megavoltage in nine studies and not stated in 12 (though it is assumed on the basis of the time period treated that these were also megavoltage; Supplementary Table 1). Two studies included a proportion of patients treated in earlier years with orthovoltage, supervoltage or radium moulds [5,37]. Radiotherapy technique was not specified in 11 studies but was 2D in six, 2D and 3D-conformal (3DCRT) in two, 3DCRT or IMRT in two and IMRT only in two. Radiotherapy dose ranged from 20 to 75 Gy (median 59 Gy) given in a median of 30 fractions over a median time of 5.8 weeks. Average dose of the four studies utilising IMRT was 61.2 Gy compared to 54 Gy in the remaining 15 studies ($P < 0.02$; unpaired t-test).

Median duration of follow-up in 18 studies ranged from 0.7 to 9.5 years (median 6.2 years) with an overall range of follow-up from 0 to 34.6 years (Table 4). Individual studies reported recurrence and survival in different ways. In 13 studies, there were 289 deaths in 696 patients (42%) with 224 due to MTC (32% of patients but 78% of all deaths). Overall survival ranged from 56 to 96% at five years (13 studies), 24 to 75% at 10 years (13 studies) and 40 to 61% at 15 years (four studies) (Table 3).

Only four studies reported actual numbers of recurrences at the primary site (i.e. local recurrence) or in nodal areas (i.e. regional recurrence), and in some studies the term local recurrence appeared synonymous with locoregional recurrence. In the 12 studies where it was reported, 24% of patients developed locoregional recurrence (range 0–55%) and 35% developed distant metastasis (range 13–58%, 11 studies; Table 4). Locoregional recurrence-free survival for whole series ranged from 54 to 87% at five years and 42 to 82% at ten years (four studies each). Some studies reported locoregional recurrence-free survival according to whether patients had received radiotherapy or not, both for whole series and selected subgroups (Table 5). In two studies of surgery 38/57 (67%) relapsed locoregionally whereas in ten studies with surgery and radiotherapy 42/196 (21%) relapsed. There was one study containing patients who were node-negative [6], and four studies with selected high-risk patients [6,16,31,33] where the effects of radiotherapy could be compared directly. In one of these four studies, there was further stratification by extent of nodal involvement [6]. In a meta-analysis, there was a 38% reduction in risk of locoregional relapse with radiotherapy (95% confidence interval 26–50%; $P < 0.00001$; Fig. 1). A high level of statistical heterogeneity was present ($I^2 = 69\%$). In one study [33], the radiotherapy group were noted to have "significantly more extracapsular extension, a higher median number of involved nodes, larger median primary and nodal sizes, and a higher incidence of mediastinal disease" underlining the unidirectional nature of the bias due to confounding. Any estimate of risk reduction due to radiotherapy therefore represents an underestimate of the true benefit.

In univariate analysis, radiotherapy had an adverse effect on overall survival in some studies [5,27,31] but no effect in others [6,11,26,36]. In multivariate analysis, radiotherapy had an adverse effect on overall survival in one study [4] but a beneficial effect in

Table 2
Retrospective series of medullary thyroid cancer showing major risk factors.

Centre/series	Years	Patients with MTC	% familial cases	Median (*mean*) age (years)	% with distant metastases	% undergoing total thyroidectomy	% with extra-thyroidal extension	% with neck dissection	% with involved nodes
Budapest [13]	1960–1999	91	37	*46*	54	18	54	33	74
Busto Arsizio [11]	1970–1972	53	17	47		32		43	
Charleroi [27]	1965–2003	44	5	54	5	100	17	75	22
French Co-operative [34]	1971–1989	59	2	*54*	0	93		86	75
Gustav Roussy [36]	1960–1983	115			11		33		57
Gustav Roussy [37]	1932–1979	75	11	*42*	17	31		55	68
Guys [35]	1974–1989	11	0	61	27	100	46	73	82
Hong Kong [16]	1960–2003	22	14	*44*	5	100	41	27	32
Lisbon [4]	1990–2000	56	14	50	9	88		59	63
Mayo Clinic [24]	1970–2007	17		*48*					
MDAnderson 1 [5]	1943–1987	202	25		9	76	18		58
MDAnderson 1a [33]	1967–1989	62			0				100
MDAnderson 2 [12]	1995–2004	34	12	48	29	100	100	100	100
MSKCC [28]	1989–2006	12							
Obninsk [25]		38							
Oporto [30]	1975–1993	12	0	43	0	58	83	58	100
Royal Marsden 1 [6]	1949–1998	162	32	44	15	80	23	32	63
Royal Marsden 1a [32]	1960–1992	51	12	45	10				80
Royal Marsden 2 [22]		7		*57*	0				
Serbia [29]	1987–1998	36	3	50		78		75	
Toronto [31]	1954–1992	73	24	49	24	56	60	51	74
Toulouse [23]	1995–2012	29	17	54	0	100	21	100	28
Vilnius [26]	1977–2006	59	5	49	0	100	58	37	37
	Overall		**19**			**84**	**46**	**58**	**71**

Table 3
Number of deaths and overall survival.

Study	Patients with MTC	Median follow-up (years)	Total number of deaths	Deaths from MTC	Overall survival			
					5 years	10 years	15 years	20 years
Budapest [13]	91	6	33	24	69	62	58	
Busto Arsizio [11]	53	4	23	20	74[a]	71[a]		
Charleroi [27]	44	7.4	15	13	76	57		
French Co-operative [34]	59	5.4	24	20	75	49		
Gustav Roussy [36]	115							
Gustav Roussy [37]	75		38	30	69	48	41	
Guys [35]	11	2.8	2	2				
Hong Kong [16]	22	9.5	7	7		75 [a]		
Lisbon [4]	56		10	10	78	65		
Mayo Clinic [24]	17	6.3						
MDAnderson 1 [5]	202							
MDAnderson 1a [33]	62	8.5						
MDAnderson 2 [12]	34	3.9			56			
MSKCC [28]	12	2.9						
Oporto [30]	12	6.5	4	4	68	42		
Royal Marsden 1 [6]	162	9	87	72	72	56	40	30
Royal Marsden 1a [32]	51	4.2	24	20	69	52		
Royal Marsden 2 [22]	7	0.7	2	2	*NR*			
Serbia [29]	36	3.2			63	24		
Toronto [31]	73	7.9						
Toulouse [23]	29	6.4			96	71		
Vilnius [26]	59	9.2	20		88	68	61	
Total	**1320**		**289/696 (42%)**	**224/696 (32%)**				
Median		**6.2**			**72**	**57**	**50**	**30**

NR not reached.
[a] cause-specific survival.

another [13]. No radiotherapy or radiotherapy to dose of less than 60 Gy were separately associated with a greater risk of local (but not regional) relapse [13] and there was a trend in favour of better local control with doses greater than 60 Gy [32]. With lower dose thresholds, radiotherapy to a dose greater or less than 45 Gy had no impact on locoregional recurrence [34] and a dose of greater or less than 55 Gy had no impact on overall survival [29]. There was a trend in favour of better progression-free survival when the interval between surgery and radiotherapy was less than two months [29].

Effects of radiotherapy on calcitonin levels were not reported. However, in two studies, calcitonin remained elevated in 21/29 and 9/11 patients despite apparently successful surgery and post-operative radiotherapy [23,35]. In a study of patients with persistently raised calcitonin post-operatively but with normal CT or MRI [38] (excluded because this study covered the same patients as reported by Hyer [6]), in only one out of six patients in whom this was measured did calcitonin normalise after radiotherapy.

Acute radiation morbidity was reported in five studies and late morbidity in seven studies (Supplementary Table 2). Toxicity was

Table 4
Incidence of locoregional and distant relapse and locoregional relapse-free survival for whole series.

Study	Evaluable patients	% receiving post-operative radiotherapy	Number with locoregional recurrence (%)	Number with distant metastases (%)	Locoregional recurrence-free survival		
					5 years	10 years	20 years
Budapest [13]	91	64					
Busto Arsizio [11]	53	15	4 (8)	8 (15)			
Charleroi [27]	44	23					
French Co-operative [34]	59	100	18 (31)	21 (36)			
Gustav Roussy [36]	115	30					
Gustav Roussy [37]	75	39	4 (7)	12 (21)			
Guys [35]	8	82	0 (0)	1 (13)			
Hong Kong [16]	22	36	7 (32)	9 (41)		82	
Lisbon [4]	56	11			72	72	
Mayo Clinic [24]	6	35	0 (0)	3 (50)	50	33	17
MDAnderson 1 [5]	202	28					
MDAnderson 1a [33]	62	37	34 (55)				
MDAnderson 2 [12]	34	100			87		
MSKCC [28]	12	100	3 (25)				
Obninsk [25]	38	5					
Oporto [30]	12	100	2 (17)	7 (58)			
Royal Marsden 1 [6]	162	47		78 (48)			
Royal Marsden 1a [32]	51	100			54	42	
Royal Marsden 2 [22]	7	100	1 (14)	1 (14)	*NR*		
Serbia [29]	36	100	10 (28)	8 (22)			
Toronto [31]	73	63					
Toulouse [23]	29	100	5 (17)	9 (31)	79	79	
Vilnius [26]	59	88					
Total			**88/362 (24%)**	**157/450 (35%)**			

NR not reached.

Table 5
Incidence of locoregional relapse and locoregional relapse-free survival (LRR) in subgroups with and without radiotherapy.

Study	Evaluable patients	Number treated with surgery only	Number with LRR	Number with surgery + radiotherapy	Number with LRR	LRR-free survival: surgery			LRR-free survival: surgery + RT		
						Number	5 years	10 years	Number	5 years	10 years
French Co-operative [34]	59			59	18						
Guys [35]	8			8	0						
Hong Kong [16]	22[b]	18	7	4	0						
Mayo Clinic [24]	6			6	0						
MDAnderson 1a [33]	62[e]	39	31	23	3	39		24	23		84
MSKCC [28]	12			12	3				12	(80)[a]	
Oporto [30]	12			12	2						
Royal Marsden 1: N0 [6]	51					38	68		13	73	
Royal Marsden 1: N1a [6]	49[c]					24	29		25	58	
Royal Marsden 1: N1b [6]	53[c]					15	29		38	60	
Royal Marsden 2 [22]	7			7	1					*NR*	
Serbia [29]	36			36	10						
Toronto [31]	73 [d]					15		52	25		86
Toulouse [23]	29			29	5				29	79	79
Total		**57**	**38 (67%)**	**196**	**42 (21%)**						

NR not reached.
[a] 2-year LRR-free survival.
[b] 41% had extrathyroidal spread, 32% involved nodes; 4 patients had radiotherapy following primary surgery and another 4 after subsequent relapse.
[c] N1a ipsilateral neck nodes; N1b contralateral, bilateral, midline or mediastinal nodes.
[d] Subgroup with any of R1 resection, involved nodes or extrathyroidal extension.
[e] Subgroup with positive nodes.

recorded prospectively in one study [22] and retrospectively in the remainder, and in a number of cases not graded. Rates of acute and late morbidity were based on 223 and 246 patients respectively, but this also included 70 patients with other types of thyroid cancer. Swallowing problems, dysphagia or the need for enteral feeding were reported in 23% acutely, but in only 6% in the longer term. Xerostomia was reported in 3% acutely and 7% long-term. Moist desquamation of the skin was recorded in 14% during or following radiotherapy, with later development of neck fibrosis in 20%. There was no clear relationship between morbidity and treatment technique expect for one study [23] reporting long-term xerostomia in 7/14 (50%) treated with 3DCRT but only 2/15 (13%) treated with IMRT ($P = 0.045$; Fisher's exact test) and neck fibrosis in 1/14 (7%) treated with 3DCRT compared to 4/15 (27%) treated with IMRT ($P = 0.21$). No study reported on quality of life after treatment.

Radiotherapy for unresectable disease

Six studies reported results of radiotherapy given as primary treatment for unresectable disease or macroscopic residual disease

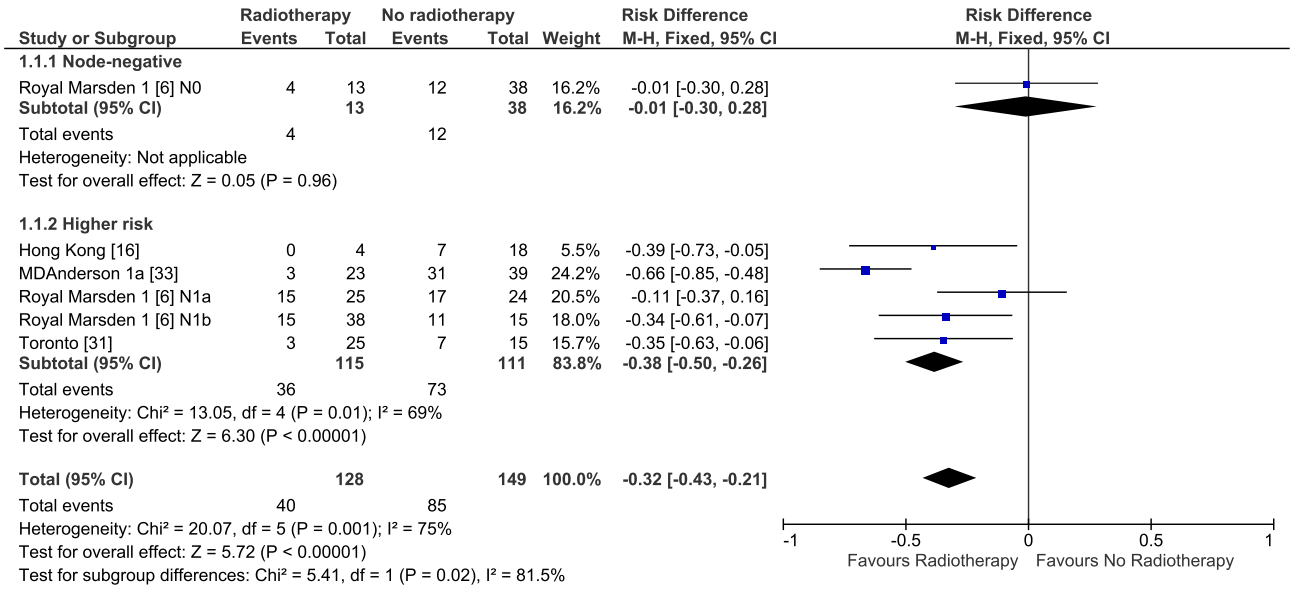

Fig. 1. Locoregional recurrence with and without radiotherapy: a meta-analysis of data from four non-randomised studies. Series or subgroups were included in the higher risk subgroup if they had involved nodes [6,33], or at least one of microscopic residual disease, extrathyroidal extension or involved nodes [16,31].

Table 6
Radiotherapy for unresectable or macroscopic residual disease.

Study	Disease extent	Number of patients	Complete response	Partial response	Stable disease	Disease progression	Not stated	5 year LRR-free survival
Gustav Roussy [36]	Unresectable at presentation	8		3	5			25%
Mayo Clinic [24]	Unresectable recurrent disease	5	3				2	67%
Obninsk [25]	Unresectable at presentation	9		5	4			ns
Royal Marsden 1a [32]	R2 resection[a]	20	6	7	6	1		25%
Toronto [31]	R2 resection	21	4				17	ns
	Total	**63**	**13 (20.6%)**	**15**[b]	**15**[b]	**1**	**19**	

ns not stated.
[a] Includes five patients with unresectable disease (with one complete response).
[b] Partial response rate 15/37 (40.5%) and disease stabilisation rate 15/37 (40.5%) if studies not reporting less than complete response rates are excluded.

(Table 6). Two studies overlapped but as Sarrazin [36] included more recent patients and excluded earlier patients (some of whom would have been treated with non-megavoltage radiotherapy), data from the earlier study [37] have not been included. Details of radiotherapy were not specified separately and assumed to be similar to those reported in Supplementary Table 1. Of these 63 patients with measurable disease, there was a complete response rate of 21% and a partial response rate of 41%. Nine of 31 (29%) were free of locoregional relapse at 5 years.

Discussion

In rare cancers, randomised studies are more difficult to design and conduct effectively and therefore recommendations for patient management need to be based on whatever data are available, however limited. Data from non-randomised studies carry a greater risk of bias which requires formal assessment. In this review, a critical risk of bias was identified in studies where a proportion of patients received radiotherapy. In the remaining studies where all patients received radiotherapy, (though formally assessed to contain a low risk of bias), the lack of clarity surrounding clinical indications for radiotherapy makes this a heterogeneous group where results of individual studies are difficult to compare.

Only 12% of patients received radiotherapy in the cohort studies in contrast to 50% of patients within the retrospective studies. The incidence of distant metastases at diagnosis was 12% in the cohort studies but up to 54% in the retrospective studies. Local spread was greater in the retrospective series (71% with nodes and 46% with extrathyroidal extension compared to 33–54% with any regional spread in the cohort studies). Compared to the cohort studies, the retrospective series therefore contained higher risk patients with both a higher rate of utilisation of radiotherapy and a worse prognosis. Many earlier studies (particularly the cohort studies) staged MTC as local, regional or metastatic. While this was standard practice at the time, it is now clear that levels of risk are related to number of nodes involved with, for example, risk of lung metastasis rising from 3% with extrathyroidal extension and 1–10 nodes involved to 13% and 28% with tumours larger than 4 cm and 11–20 or more than 20 nodes involved [8]. As development of distant metastases and risk of subsequent death are related to the extent of nodal involvement [8,9], it would be expected that overall or cause-specific survival would be worse in subgroups receiving radiotherapy, as seen in earlier studies [5].

The response rate of MTC to radiotherapy in unresectable and R2 patients shows that radiotherapy is an effective treatment modality in a proportion of patients. As in other cancer types, one might expect the margin of gain to be greater where there is

only microscopic disease at the time of treatment. In this review, fewer locoregional relapses were seen after post-operative radiotherapy. Although many studies in this review were judged to be at critical risk of bias, this bias would be in favour of surgery alone - reducing the apparent degree of benefit from radiotherapy. In four studies, with a degree of balance of risk factors, although not randomised, it was felt that meta-analysis was justified to obtain a combined estimate. The effects of bias are such that the estimated risk reduction of 38% is likely be an under-estimate.

It is noteworthy that higher radiation doses were used in IMRT studies compared to earlier techniques and that two studies identified doses greater than 60 Gy as more effective [13,32]. One study reported increased locoregional relapse rates following delays in starting radiotherapy [29]. This is consistent with observations in head and neck cancer where it is recommended that radiotherapy should start within six weeks of surgery [39].

In one study, there was a greater incidence of distant metastasis in those with locoregional relapse [33], so it is possible that locoregional recurrence, although rarely directly fatal [33], might provide a further opportunity for cancers to metastasise, and reducing this risk might then result in a small survival benefit. While the evidence is consistent with radiotherapy having no significant effect on overall survival, the possibility of a small survival benefit cannot be entirely excluded.

There were limited data in relation to the effects on serum calcitonin, except that in locoregional disease the majority continue with persistently raised calcitonin despite radiological evidence of complete response.

Rates of treatment-related morbidity were based on a minority of patients (246/670, 37%), varied between studies and were often not graded, and so represent a limited view of the effects of treatment. Furthermore, only 82 patients were in studies where IMRT was used (though not all had received IMRT), so it is difficult to reach conclusions relevant to current practice where IMRT should be the norm. In the Toulouse series [23] where approximately half were treated with IMRT, there was more neck fibrosis and less xerostomia with IMRT compared to 3DCRT.

Conclusions

External beam radiotherapy reduces the risk of locoregional relapse by at least 38% and improves locoregional relapse-free survival, particularly in high-risk patients, but without consistent effect on overall survival. The effects of bias are considered likely to result in an under-estimate of benefit.

Implications for practice

External beam radiotherapy to a dose of at least 60 Gy and started within 6–8 weeks of surgery should be considered for those with lymph node involvement, extrathyroidal extension or residual disease (microscopic or macroscopic), with higher doses considered for those with unresectable disease (either as primary treatment of for recurrence) or macroscopic residual disease. IMRT should be used to minimise the dose to adjacent normal tissues. In the future, the development of more effective systemic therapies may increase the importance of locoregional control, with a greater emphasis on post-operative radiotherapy.

Implications for research

Uncertainties remain concerning the precise level of risk reduction of locoregional recurrence following radiotherapy and the threshold for recommending radiotherapy with respect to the number of risk factors present. Multicentre randomised trials would be ideal in this situation but the practicalities present significant challenges. Retrospective studies from large centres or cooperative groups can be helpful, provided risk factors are specified in much greater detail. Further development of staging systems would support better treatment stratification.

Conflicts of interest

There are no conflicts of interest.

Funding sources

Dr N P Rowell is employed by Maidstone & Tunbridge Wells NHS Trust.

There are no additional sources of funding.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.033.

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