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REVIEW ARTICLE

The role of adjuvant radiotherapy in management of recurrent pleomorphic adenoma of the parotid gland: a systematic review

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Abstract

Purpose Recurrent pleomorphic adenoma poses a significant treatment challenge, considering its propensity for further recurrence and potential for malignant transformation. The role of adjuvant radiotherapy in its management is widely debated. The aim of this study was to determine whether adjuvant radiotherapy is more effective than surgical resection alone in patients with recurrent pleomorphic adenoma of the parotid gland, in terms of further recurrence, malignant transformation and treatment-related complications.

Methods Using PRISMA guidelines, a systematic review comparing adjuvant radiotherapy with surgery alone in the treatment of recurrent pleomorphic adenoma was conducted. Pubmed, OVID, EBSCO, Embase, The Cochrane Library, SCOPUS and OpenGrey databases from 1988 to 2018 were searched. Quality analysis was carried out using the Newcastle–Ottawa Scale and narrative synthesis used to summarise results.

Results Of 891 records screened, eight studies were included, assessing 366 participants. Two noted a benefit of adjuvant radiotherapy in reducing further recurrence. The remainder did not show significant benefit, although four showed a trend towards lower rates. Only one case of malignant transformation was identified in a patient not irradiated. Similar rates of facial nerve dysfunction were identified between groups.

Conclusion The available evidence suggests that adjuvant radiotherapy reduces recurrence rates in patients with recurrent pleomorphic adenoma and certain adverse prognostic factors. While it appears not to have significant adverse effects, given the lack of prospective evidence, we recommend careful use in patients at high risk of further recurrence and further research in the form of well-designed randomised controlled trials.

Keywords Pleomorphic adenoma · Radiotherapy · Recurrence · Malignant transformation · Facial weakness

Introduction

Pleomorphic Adenoma is the most common salivary gland neoplasm, affecting approximately 2–3.5 people per 100,000 per year [1]. It is most commonly found in the superficial lobe of the parotid gland, but can affect the minor salivary glands or lacrimal gland of the eye [1, 2].

Although it is a benign neoplasm, prompt surgical excision is the standard of care. Aside from its cosmetic impact, it has a potential for malignant transformation, in the form of carcinoma ex-pleomorphic adenoma, with transformation rates reported between 1 and 23% [3]. This risk increases with time and number of recurrences [3]. 5 year survival rates of carcinoma ex-pleomorphic adenoma are reported as 25–75%, a worse prognosis than most other salivary gland malignancies [4].

The United Kingdom National Multidisciplinary Guidelines recommend complete excision for all first-presentation pleomorphic adenomas, with no need for routine adjuvant treatment [5]. Options include enucleation—a procedure which has fallen out of favour due to high recurrence rates-superficial parotidectomy or total parotidectomy. Recently, extracapsular dissection has become more common, involving excision of the encapsulated tumour with a rim of healthy tissue, without dissection of the nerve [6].

Pleomorphic adenomas have a propensity for local recurrence, with rates ranging from 20 to 45% after enucleation to between 2 and 5% following superficial parotidectomy [6]. At

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present, there is no standard of care for recurrent neoplasms. While these are often treated with repeated excision, rates of further recurrence have been reported as high as 50% [7]. With each re-operation, likelihood of further recurrence and morbidity, in particular, risk of facial nerve dysfunction increases [7]. This may occur as a result of tumour invasion and subsequent sacrifice during excision, or due to inadvertent intra-operative insult. With repeated intervention, build up of scar tissue makes dissection of the tumour off the nerve more difficult, and injury more likely. Both rates of temporary and permanent dysfunction are higher in those undergoing repeated procedures, with temporary nerve palsy occurring in 90–100%, compared with 9.1–64% of those with no history of prior parotid surgery [3]. Permanent palsy is reported to occur in 0–3.9% of patients initially treated for pleomorphic adenoma, and up to 40% of those undergoing surgery for recurrence [3].

Facial nerve palsy is a debilitating complication, having a range of functional, social and psychological consequences. Functionally, an inability to close the eye, leads to dry eye, corneal abrasion and damage [8]. Socially, impaired facial expression can result in communication difficulties [9]. Psychologically, disfigurement may lead to distress, anxiety and depression [9].

Post-operative radiotherapy has been suggested for use in recurrent pleomorphic adenoma, with some studies showing benefit in improving local control and decreasing further recurrences [7, 10, 11]. However, there have been suggestions that it may negatively impact recovery of facial nerve neuropraxia, increase rates of malignant transformation and increase risk of late-term secondary malignancies [7, 11, 12]. The incidence of radiation-induced malignancy is estimated to be in the range of 0.4–1% [13]. As the prognosis tends to be poor, with 5 year survival less than 30% [13], it is understandable that there are concerns irradiating these generally young patients for a benign disease process.

The treatment of recurrent pleomorphic adenoma of the parotid gland poses a significant challenge, considering its propensity for recurrence, lack of clear guidelines, and debate regarding the role of adjuvant radiotherapy. Therefore, the aim of this study was to determine whether adjuvant radiotherapy is more effective than surgical resection alone in patients with recurrent pleomorphic adenoma of the parotid gland, in terms of further recurrence, malignant transformation and treatment-related complications.

Methods

Study design

This was a systematic review using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) guidelines [14].

Information sources

Two independent reviewers (LM and SG) carried out a search of the Pubmed, OVID, EBSCO, Embase, The Cochrane Library, SCOPUS and OpenGrey databases. The literature search was limited to studies published in the last 30 years. This time frame was chosen to minimise the effect of outdated surgical practices [15] on our results.

Search strategy

The two reviewers cross-searched the following terms for each of the seven databases:

Recurrent	*And*	Pleomorphic adenoma	*And*	Management
		Salivary gland tumour		Treatment
				Radiotherapy
				Radiation therapy
				Neutron radiation

Eligibility criteria

Studies were included if they met the following criteria:

1. The study was a randomized controlled trial, non-randomized controlled trial, prospective or retrospective cohort study.
2. The study reported on outcomes in patients treated for recurrent pleomorphic adenoma of the parotid gland.
3. The study compared benefits and adverse effects of surgery alone and surgery combined with adjuvant radiotherapy.

Studies were excluded if:

1. It reported on outcomes in patients treated with primary rather than adjuvant radiotherapy.
2. It had no comparison group.
3. It was a case report or abstract with insufficient data for inclusion.
4. There was no English translation available.

Study selection

The articles found on initial search underwent a two-stage screening process. In the first, titles and abstracts were reviewed, duplicates removed and those not meeting the inclusion criteria excluded. In the second, full text articles were obtained and studied. Eligibility assessment was

performed independently by the two reviewers and disagreements resolved by discussion.

Data collection

Data were extracted into purpose-built data sheets by the first author (LM) and checked with the second (SG). Additional information from authors of the studies was not required. Data collected included; inclusion and exclusion criteria, type of intervention and comparison treatments, sample sizes, length of follow up, outcomes, patient and tumour variables and study conclusions.

Quality appraisal

The Newcastle–Ottawa Scale for Cohort Studies [16] was used to assess quality of the included studies. It assigns a maximum of nine points under three domains; selection, comparability and outcome. The reviewers agreed on methods and criteria for scoring prior to independent assessment.

The selection domain assesses whether participants have been selected without bias. Studies were awarded points if they included all patients treated during the study period and demonstrated that the outcome of interest was not present at the beginning of the study, in this case, by showing that patients did not have residual disease following treatment for initial recurrence.

The comparability domain assesses whether groups are matched in design or confounders adjusted for. Here, the confounding factors were age, gender, tumour multifocality, multiple previous recurrences, and initial surgical procedure—each significant prognostic factors [6, 17–19].

Studies scored well in the outcome domain if they assessed outcomes in a non-biased manner, using reliable sources, and provided sufficient length of follow-up while accounting for the majority of participants. The minimum follow-up period required for assessment of outcomes was 10 years, based on mean time to recurrence across a number of studies [20].

Synthesis of results

Our primary outcome was further disease recurrence following treatment. This was measured by calculation of recurrence rates between groups treated with adjuvant radiotherapy and those treated with surgical excision alone in each study.

Secondary outcomes included malignant transformation to carcinoma ex-pleomorphic adenoma, and treatment complications—facial weakness and secondary radiation-induced malignancy.

A narrative analysis was used to summarise characteristics and outcomes of the included studies. As all eligible studies were retrospective studies with a high level of clinical heterogeneity, meta-analysis was felt to be inappropriate.

Results

Search and study selection

Seven databases were searched: Pubmed, OVID, EBSCO, Embase, The Cochrane Library, SCOPUS and OpenGrey, yielding 2888 results. After duplicates were removed, 891 studies remained. On screening tites and abstracts of these studies, 850 did not meet our inclusion criteria, and 41 were selected for full text review.

Following this, a further 33 were excluded for various reasons, outlined in Fig. 1. Seven studies met the inclusion criteria. One further study was identified by cross-checking articles citing and the references of the included studies. Overall, eight studies were included.

Study characteristics

All eight were retrospective cohort studies. No randomised controlled trials or prospective studies were identified. Characteristics of the studies are shown in Table 1.

A total of 366 participants were included, with numbers in each study ranging from 22 to 114. All studies included patients undergoing treatment for recurrent pleomorphic adenoma. Liu et al. [21], studied those with recurrent pleomorphic adenoma as a sub-set of patients treated for benign parotid tumours. Exclusion criteria varied between studies. Overall, 208 participants were female and 125 were male. Data regarding gender was unavailable for the 33 patients from Liu et al. Studies were carried out across five geographical locations, three in the USA [10, 12, 22], two in France [17, 18], and the remainder in Canada [21], Israel [23] and Italy [19].

Characteristics of the participants in each of the studies are shown in Table 2. Three noted that a higher percentage of patients in the adjuvant radiotherapy group had one or more previous recurrences. Abu-Ghanem et al., found that 77.8% in the radiotherapy group was undergoing treatment for a second recurrence compared with 30.8% in the surgery alone group. In Carew et al., these figures were 73% vs 35% and in Makeieff et al., 100% vs 17%.

Renehan et al. reported that 62.7% in the group treated with adjuvant radiotherapy had multifocal recurrence compared with 31.7% in those not irradiated. Makeieff et al. did not report this figure in those undergoing surgery alone, however, noted that all patients undergoing adjuvant radiotherapy had a multifocal recurrence, higher than the overall rate of 63%.

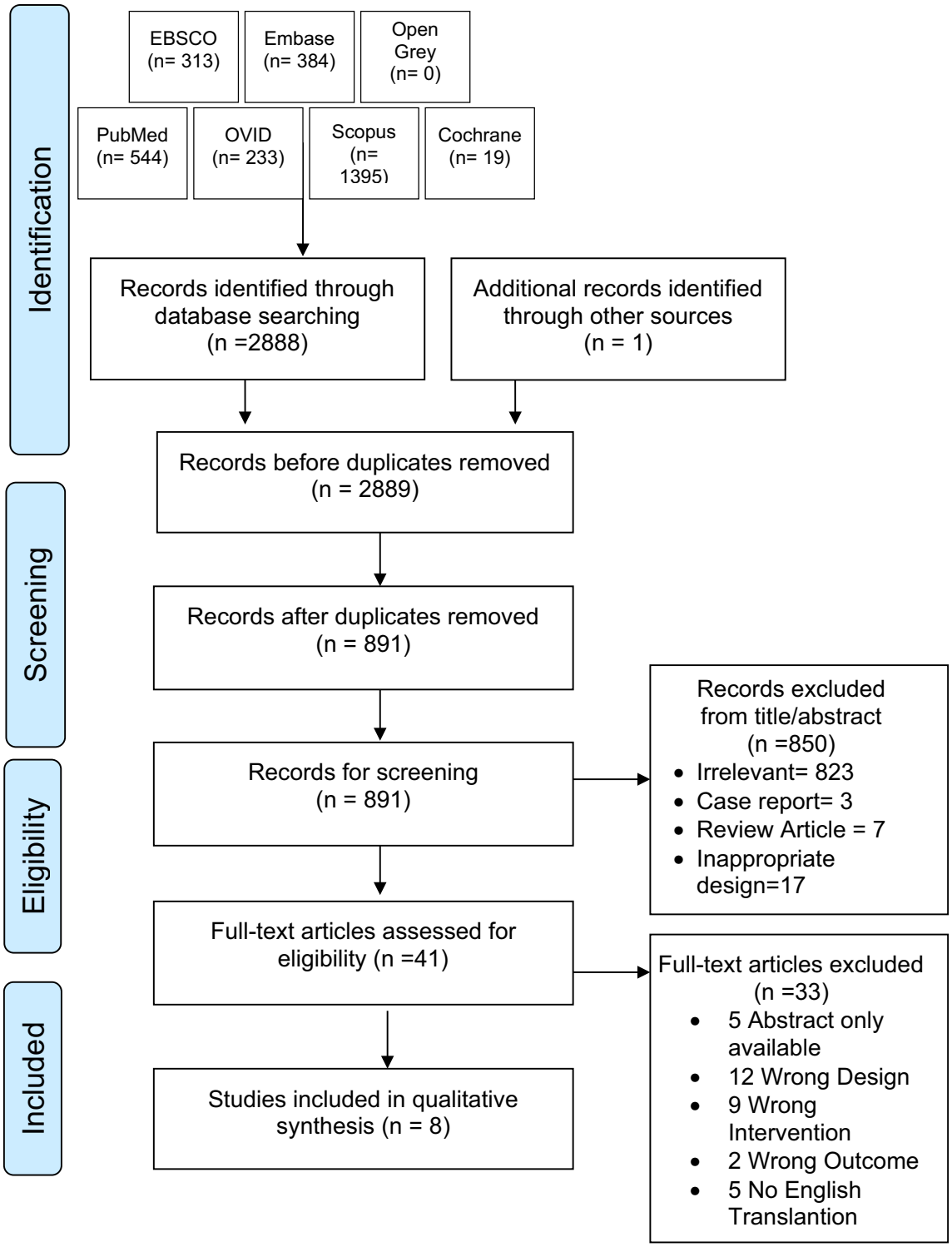

Fig. 1 PRISMA flowchart of study selection

Carew et al., found that a higher percentage of patients treated with radiotherapy had positive margins following excision—36.4% vs 5%.

None reported on the variation in initial surgical treatment between the two groups.

In each study, the intervention consisted of surgical excision followed by adjuvant radiotherapy while the control

Table 1 Characteristics of included studies

Study ID location	Study design and data period	Inclusion criteria and sample size	Exclusion criteria	Intervention	Comparison	Primary outcome	Mean age (years)	Gender	
								Male	Female
Malard 2013 France	Retrospective cohort 1988–2008	32 patients with RPA	Non-parotid pleomorphic adenoma	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence	Mean 41.3	16 (50%)	16 (50%)
Abu-Ghanem 2016 Israel	Retrospective cohort 1991–2013	22 patients treated for RPA	Nil	Surgery and adjuvant radiotherapy	Surgery alone	Recurence	Mean 43.5	8 (40%)	14 (60%)
Renehan 1996 USA	Retrospective cohort 1952–1992	114 patients with first pleomorphic adenoma recurrence	1. Multiple prior operations 2. Residual disease	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence: cumulative rate at 15 years	Median 45	37 (32%)	77 (68%)
Carew 1999 USA	Retrospective cohort 1984–1993	31 patients undergoing surgery for RPA	Inadequate follow-up	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence	Median 44	10 (32%)	21 (68%)
Liu 1995 Canada	Retrospective cohort 1970–1987	76 patients treated for benign parotid tumours 33 with RPA	1. Tumours of minor salivary glands 2. No follow-up information 3. Concurrent pathologies 4. Malignancy 5. Received RT elsewhere	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence: 10 year relapse free rate	Median 25 years	n/a	n/a
Redaelli de Zinis 2008 Italy	Retrospective cohort 1983–2004	33 patients operated on for RPA	Nil	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence: estimated rate at 5/10/15/20 years	Median 41 (12–71)	15 (45.5%)	18 (54.5%)
Makeieff 2010 France	Retrospective cohort 1982–2008	62 patients operated on for RPA	Patients undergoing surgery for residual disease	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence	Median 47.5 (17–78)	27 (43.5%)	35 (56.5%)
Yugeros 1998 USA	Retrospective cohort 1965–1993	39 patients with RPA treated by single surgeon	Nil	Surgery and adjuvant radiotherapy	Surgery alone	Recurrence	Mean 50	12 (31%)	27 (69%)

RPA recurrent pleomorphic adenoma, *RT* radiotherapy

Table 2 Characteristics of study participants

Study ID	Tumour characteristics						Treatment characteristics		
	> 1 previous recurrence		Multifocal tumour		Positive margins		Type of initial surgery		
	S + RT	S	S + RT	S	S + RT	S	Local excision	Superficial parotidectomy	Subtotal/total parotidectomy
Malard 2013	15 46.9%		18 56.3%		–	–	18 56%	10 31%	4 13%
Abu-Ghanem 2016	7 77.8%	4 30.8%	15 68.2%		–	–	2 9%	19 86%	1 5%
Renehan 1996	0	0	32 62.7%	20 31.7%	–	–	67 59%	5 (4%) any parotidectomy 37 (32%) unknown	
Carew 1999	8 73%	7 35%	17 54.8%		4 36.4%	1 5%	15 50%	13 43.3%	2 6.7%
Liu 1995	15 45%		–	–	–	–	–	–	–
Redaeli 2008	12 36.36%		24/31 77.4% 2 unknown		8/31 25.8% 2 unknown		11 33.3%	7 21.2%	11 33.3%
Makeiff 2010	5 100%	8 17%	5 100%	Overall 39/62 63%	–	–	16 25.8%	31 50%	15 24.2%
Yugeros 1998	–	–	–	–	–	–	–	–	–

S + RT surgery and adjuvant radiotherapy (intervention), *S* surgery alone (comparison)

groups received surgery alone. However, the type of surgical intervention performed and radiotherapy used varied between studies. Surgical treatments included enucleation, extracapsular dissection, superficial or total parotidectomy and varied considerably between studies. The majority did not differentiate between enucleation and extracapsular dissection, classifying treatment as local excision or parotidectomy. Liu et al. did not report on the type of surgical intervention performed. Only Yugeros et al. reported the variation in surgical treatments between the intervention and control groups.

Four studies [12, 17–19] did not comment on the type or dose of radiotherapy used. There was significant heterogeneity within the remainder, with Renehan et al. and Liu et al. reporting variation in the type of radiotherapy used as practices changed over the course of the study. In Abu-Ghanem et al., the technique used varied depending on the time of treatment, extent of disease and treating clinician preferences. Further details on the interventions performed in each study are presented in Table 3.

While recurrence was the primary outcome in each of the studies, the role of adjuvant radiotherapy was not the main focus in any, and instead reported as part of a larger analysis assessing prognostic factors for further recurrence of pleomorphic adenoma. Five studies [12, 17, 18, 22, 23] reported this as a percentage recurrence rate, while Liu et al. reported recurrence in terms of 10 year relapse free rate, Redaelli de Zinis et al. reported the estimated recurrence rate at 5, 10, 15 and 20 years and Renehan et al. reported the cumulative recurrence rate at 15 years.

Quality analysis

Quality analysis scores using the Newcastle–Ottawa Scale for Cohort Studies [16] ranged from 3 to 7 points, with six studies scoring 5 points from a maximum of 9. None were excluded due to poor quality. Once the method and criteria for scoring was decided on by the reviewers, there were no disagreements. Details of the scoring for each study is shown in Table 4.

Selection

Six studies [10, 12, 18, 21–23] scored three out of four points for selection, as none clearly stated that patients were disease-free following initial treatment. The remainder [17, 19] scored two points, as it was not clear if the study population included all patients treated for recurrent pleomorphic adenoma and, therefore, truly representative of the average cohort with the condition.

Table 3 Interventions

Study ID	Type of surgery for recurrence						Type of radiotherapy given	Dose of radiotherapy
	Local excision (enucleation/ extra-capsular dissection)		Superficial parotidectomy		Subtotal/total parotidectomy			
	S + RT	S	S + RT	S	S + RT	S		
Malard 2013	5 15%		3 10%		24 75%		–	–
Abu-Ghanem 2016	22 100%		0 0%		0 0%		Technique not specified Continuous course	Median 5000 cGy range 4500–6000 cGy
Renehan 1996	33 29%		54 47%		27 24%		21 Intraoperative implant 30 External beam radiation	60 Gy for implant 50 Gy for external beam
Carew 1999	6 19.4%		6 19.4%		19 61.3%		External beam radiation to parotid bed	Median 5580 cGY range 5400–6300 cGy
Liu 1995	–	–	–	–	–	–	31 Direct lateral field using electrons 22 Wedged pair technique using photons 2 Mixed proton and electron beam	Median 47.33 Gy range 28.56–60.96 Gy
Redaeli de Zinis 2008	7 21.2%		10 30.3%		16 48.5%		–	–
Makeieff 2010	16 25.8%		3 4.8%		43 69.4%		–	–
Yugeros 1998	9 23.1%	5 12.8%	3 7.6%	22 56.4%	0 0%	0 0%	–	–

S + RT surgery and adjuvant radiotherapy (intervention), *S* surgery alone (comparison)

Table 4 Newcastle–Ottawa quality assessment of studies

Study ID	Selection				Comparability	Outcome			Total score
	Representative-ness of Intervention Cohort	Selection of non-intervention cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Sufficient follow-up time	Adequacy of follow up	
Malard 2013	–	*	*	–	–	*	–	–	3
Abu–Ghanem 2016	*	*	*	–	–	*	*	–	5
Renehan 1996	*	*	*	–	**	*	*	–	7
Carew 1999	*	*	*	–	–	*	–	*	5
Liu 1995	*	*	*	–	–	*	*	–	5
Redaeli 2008	–	*	*	–	–	*	*	*	5
Makeieff 2010	*	*	*	–		*	–	*	5
Yugeros 1998	*	*	*	–	–	*	*	–	5

Comparability

Only Renehan et al., scored two points, having controlled for two important confounding factors—tumour multifocality and number of previous recurrences.

Outcome

Redaelli de Zinis et al., scored the maximum three points, indicating that outcomes were assessed in a reliable and unbiased manner and all participants were followed up for an adequate length of time. Six studies [10, 12, 18, 21–23] scored two points and one—Malard et al., scored one point, due to inadequate follow-up time and uncertainty as to whether all participants were accounted for.

Synthesis of results

Results of the eight studies are summarised in Table 5.

Recurrence

All studies reported on rates of further recurrence in patients treated for recurrent pleomorphic adenoma. Two [10, 21] reported a benefit in the use of adjuvant radiotherapy for this patient cohort, while six found no significant difference.

Renehan et al. found that the 15 year cumulative recurrence rate for patients treated with adjuvant radiotherapy was 4%, compared with 24% in those treated with surgery alone ($P=0.01$). They then analysed patients with multinodular and uninodular recurrences, finding that those with multinodular recurrences had a recurrence rate of 43% at 15 years when treated with surgery alone, versus 4% when treated with adjuvant radiotherapy ($P=0.008$). In contrast, this rate was 15% for uninodular recurrences when treated with surgery alone, and 13% with adjuvant radiotherapy ($P=0.9$). Overall, they concluded that multinodular recurrences of pleomorphic adenoma benefit from adjuvant radiotherapy while uninodular recurrences may be treated with surgery alone.

Liu et al. found the recurrence rate in those treated with adjuvant radiotherapy to be 18.75% (3 of 16) versus 94% (16 of 17) in those not irradiated, reported as a 10 year relapse free rate of 75% vs 25%, respectively ($P=0.0001$), leading the authors to recommend the use of adjuvant radiotherapy.

The remaining six studies did not find a statistically significant benefit of adjuvant radiotherapy in reducing recurrence, though four showed trends towards lower recurrence rates in patients receiving radiotherapy.

Abu-Ghanem et al. found a 22% (2 of 9) recurrence rate in the radiotherapy group, compared with 31% (4 of 13) for surgery alone, a difference that was not statistically significant. They concluded that radiotherapy should only be recommended in patients who have had two or more recurrences where the facial nerve is at risk and chances of further recurrence are high.

In Carew et al., no patient had further recurrence following adjuvant radiotherapy, while 3 of 20 (15%) had a recurrence following surgery alone. While this difference was not significant ($P=0.28$), they felt that better local control was achieved with radiotherapy.

Redaelli de Zinis et al. found that the recurrence rate in the irradiated group was 22.2% compared with 37.5% in the non-irradiated group ($P=0.3$). They calculated the estimated tumour recurrence rate at 5 years in the group treated with adjuvant radiotherapy and those treated without, to be 12.5% vs 14.2%, respectively. At 10 years this was 25% vs 34.3% and at 20 years 25% vs 65.9%, leading them to suggest postoperative radiotherapy as an option for treatment of recurrent pleomorphic adenoma despite the lack of statistical significance.

Makeieff et al. found no recurrences among the 5 patients with benign recurrent pleomorphic adenoma treated with adjuvant radiotherapy, all of whom had multifocal tumours and positive margins, while the recurrence rate in the comparison group was 12.8% (6 of 47). However, this difference was not significant ($P=0.73$) and the authors felt that it was not possible to draw conclusions regarding the benefit of adjuvant radiotherapy.

Malard et al. reports a 27.27% (3 of 11) recurrence rate in the adjuvant radiotherapy group vs 28.51% (6 of 21) in patients not irradiated, concluding that the lack of benefit of radiotherapy ($P=0.8$), may be due to the small study size.

Finally, Yugeros et al. reported a 33.3% recurrence rate in 12 patients treated with adjuvant radiotherapy and a 14.8% rate in the 27 patients treated with surgery alone ($P>0.05$). They concluded that small numbers did not allow for conclusions to be drawn regarding the use of radiotherapy.

Malignant transformation

Four studies [18, 19, 21, 23] reported on the rate of malignant transformation to carcinoma ex-pleomorphic adenoma. Of these, three found no cases of malignant transformation in either group. Makeieff et al. found that two patients developed carcinoma in further recurrences. One was found in a recurrence of a benign tumour previously treated with surgery alone, while the other was a recurrence of a previously diagnosed carcinoma ex-pleomorphic adenoma treated with radiotherapy. There were no cases of malignant transformation in the five patients treated with adjuvant radiotherapy for benign recurrent pleomorphic adenoma.

Table 5 Results

Study ID	No of patients: intervention	No of patients: comparison	Length of follow up	Outcomes							
				1. Recurrence		2. Malignant transformation		3. Facial weakness[a]		4. Further malignancy	
				S + RT	S	S + RT	S	S + RT	S	S + RT	S
Malard 2013	11	21	Mean 9.7 years	3 27.3%	6 28.6%	–	–	10 (31%) persist > 1 year 2 intentional sacrifice		–	–
Abu-Ghanem 2016	9	13	Median 140 months	2 22%	4 31%	0	0	2 (9%) permanent		–	–
Renehan 1996	51	63	Median 14 years (1–35)	8% Cumulative recurrence at 15 years	24% Cumulative recurrence at 15 years	–	–	5 (11%) permanent 15 (32%) temporary 4 intentional sacrifice	6 (15%) permanent 22 (36%) temporary 2 intentional sacrifice	–	–
Carew 1999	11	20	Median 88 months	0 0%	3 15%	–	–	14/24 (58%) temporary 2/24 (8%) permanent 5 Pre-operative weakness 2 Intentional sacrifice		–	–
Liu 1995	16	17	Median 12.5 years	3 18.8%	16 94%	0	0	7 (21%) temporary 5 (15%) permanent		0	0
Redaelli de Zinis 2008	9	24	Median 10.5 years (2–25)	2 22.2%	9 37.5%	0	0	7/23 (30.4%) temporary 1/23 (4.3%) permanent 10 Intentional sacrifice		3 10%	
Makeieff 2010	5 Benign RPA 10 CEPA	47	Median 9 years (4–28)	0/5 0%	6 12.8%	0 Benign RPA 1 CEPA	1 2.1%	50/53 (95%) temporary 7/53 (11.3%) persist > 1 year		–	–
Yugeros 1998	12	27	Mean 10 years	4 33.3%	4 14.8%	–	–	1 23%	0	–	–

S + RT surgery and adjuvant radiotherapy (intervention), *S* surgery alone (comparison), *CEPA* carcinoma ex-pleomorphic adenoma, *RPA* recurrent pleomorphic adenoma

[a]Facial weakness (%) excludes cases where nerve is deliberately sacrificed and patients with pre-operative weakness

Facial weakness

While all studies assessed rates of facial nerve dysfunction in patients undergoing treatment for recurrent pleomorphic adenoma as a whole, only two [10, 12] reported on differences between the two groups.

For reporting of this complication, we excluded cases where dysfunction existed pre-operatively or where the nerve was deliberately sacrificed.

Yugeros et al. found that 1 of 12 patients (23%) treated with adjuvant radiotherapy developed facial paralysis, with onset after completion of radiotherapy. No patient treated with surgery alone developed facial nerve dysfunction.

Renehan et al. found that 15 of 47 (32%) of patients in the radiotherapy group developed temporary weakness, while 5 (11%) suffered permanent dysfunction. In the group not irradiated, 22 of 61 (36%) experienced a transient palsy, with 9 (15%) developing permanent weakness. Of note, six others had deliberate sacrifice of the nerve, four in the radiotherapy group (8%) and two in the comparison group (3%).

Secondary malignancy

The incidence of secondary malignancy was assessed in two studies [19, 21]. Liu et al. found no cases of malignancy in patients in either treatment group followed up over a median time period of 12.5 years.

Meanwhile, Redaelli de Zinis et al., found that 3 of 33 (10%) participants developed metachronous malignancy. However, they did not differentiate between those who had received adjuvant radiotherapy and those who had not, nor did they report on the type of malignancy developed.

Discussion

The management of recurrent pleomorphic adenoma of the parotid gland is a challenging issue with rates of further recurrence reported as high as 45% [3]. With each further recurrence, comes an increased risk of morbidity, a decreased likelihood of local control and increased risk of malignant transformation. The role of radiotherapy is debated.

Of the eight studies, the two largest [10, 21] found that adjuvant radiotherapy reduced the rate of further recurrence. While the remainder failed to demonstrate a significant benefit for radiotherapy, four showed a trend towards lower recurrence rates. None found an adverse effect of radiotherapy on recurrence.

Recurrence rates ranged from 0 to 33% in the adjuvant radiotherapy group, and from 12.8 to 37.5% in the surgery only group.

Renehan et al., in addition to noting an overall benefit of adjuvant radiotherapy in reducing further recurrence, found that those with multinodular recurrences benefited proportionately more than those with uninodular recurrence, having a significantly lower recurrence rate of 4% at 15 years following adjuvant radiotherapy vs 43% when treated with surgery alone. The difference in those with uninodular recurrences, at 15% at 15 years with surgery alone, and 13% with adjuvant radiotherapy, was not significant.

No randomised controlled trials evaluating adjuvant radiotherapy vs surgery alone in the treatment of recurrent pleomorphic adenoma exist and much of the literature relating to the efficacy of radiotherapy in reducing recurrence rates exists in the form of relatively small case-series with no control group.

Chen et al. [7], found a 20 year local control rate of 94% in patients with recurrent pleomorphic adenoma treated with adjuvant radiotherapy. Many of the 34 patients in this study had adverse prognostic factors, with 47% having multifocal disease, and only 24% undergoing treatment for a first recurrence. Ravasz et al. [24], reported similar findings with only one further recurrence among 16 patients (6.25%) treated for recurrent tumours. Bucholz et al. [25], found no further recurrences over 11 years in a series of six patients. Dawson et al. [11], report a 10% recurrence rate among 20 patients treated for first recurrence of pleomorphic adenoma with adjuvant radiotherapy, while Samson et al. [26], reported a local control rate of 81% among 21 patients receiving adjuvant radiotherapy, all of whom had residual disease following surgery. In each study, authors felt that adjuvant radiotherapy conferred benefit in reducing further recurrence.

Overall, it appears that radiotherapy is effective in reducing recurrence rates in certain patients with recurrent pleomorphic adenoma, namely those with adverse prognostic factors such as multinodular recurrence.

Malignant transformation

Development of carcinoma in a benign pleomorphic adenoma is reported to occur in 1–23% [3] of patients, with risk proportional to time and number of recurrences of the neoplasm. Amongst the 4 studies reporting on rates of malignant transformation to carcinoma ex-pleomorphic adenoma, 140 patients were assessed and only one case identified, occurring in a patient treated with surgical excision alone. Given the small numbers, it is not possible to draw conclusions regarding the effect of adjuvant radiotherapy on rates of malignant transformation.

Facial weakness

Facial nerve dysfunction is a complication of repeated surgical excision of pleomorphic adenoma. Rarely it occurs as a result of direct tumour invasion, and more commonly due to deliberate sacrifice during excision or as a result of accidental injury. Repeated procedures make dissection of the tumour off the nerve more difficult, and injury more likely [3]. It has been suggested that radiotherapy may delay the recovery of temporary facial nerve neuropraxia [12]. Only one patient from Yugeros et al., treated with adjuvant radiotherapy developed facial paralysis following completion of radiotherapy. Renehan et al. found similar rates of temporary and permanent dysfunction between the two groups, with a 32% rate of temporary paresis in patients in the adjuvant radiotherapy group compared with 36% in those treated with surgery alone. The rate of permanent palsy was 11% and 15%, respectively. Notably, a higher rate of deliberate sacrifice occurred in patients undergoing radiotherapy (8% vs 3%), likely due to the more complex nature of tumours in these patients.

Little conclusion can be drawn from Yugeros et al., however, based on the findings in the larger study by Rehehan et al., radiotherapy does not appear to have a detrimental effect on facial nerve function or recovery. Likewise, previous studies [27, 28] assessing the effect of radiotherapy on facial nerve graft repair, have found that radiotherapy has no adverse effect on functional outcomes.

Radiotherapy has been shown to induce fibrosis of the parotid gland [29]. The likelihood of nerve injury is directly related to the level of scarring of the gland with dense fibrosis predisposing to nerve injury. Renehan et al. found the rate of permanent nerve palsy as high as 30% in patients undergoing third reoperation for pleomorphic adenoma, however, none of the studies comments on the rates of nerve injury in patients experiencing recurrence following treatment with adjuvant radiotherapy. Indeed, no literature exists comparing rates of facial nerve injury in salvage parotid surgery in irradiated and non-irradiated patients.

Secondary malignancy

One concern surrounding the use of radiotherapy in these benign neoplasms is the theoretical risk of secondary malignancy in the longer term. The incidence of radiation-induced malignancy is relatively unknown, estimated to be in the range of 0.4–1% [13] and prognosis is poor, with 5 year survival less than 30% [13]. As patients developing recurrent pleomorphic adenoma are generally young, with median ages across our included studies ranging from 25 years to 47.5 years, there are understandable concerns in irradiating these patients with significant life-expectancies for a benign condition.

Based on our findings, in which only three participants from two studies [19, 21] developed metachronous malignancy, and the authors did not differentiate between those receiving radiotherapy and those not, it is not possible to draw conclusions regarding the risk of radiation-induced malignancy.

Previous studies on radiation-induced malignancy of the head and neck found that the mean time to diagnosis of malignancy following exposure ranged from 22 to 36.5 years [13, 30, 31]. Miyahara et al. [30] identified 65 patients with radiation-induced cancers of the head and neck, of which 48 had been irradiated for benign disease. While the mean time from exposure to the diagnosis of malignancy in patients treated for malignant tumours was 12.8 years, the time taken for secondary malignancy in patients irradiated for benign disease to manifest was much longer at 32.9 years, likely due the use of more aggressive regimens for malignant disease. The median length of follow up in the studies included in our review ranged from 7.3 to 14 years, meaning the possibility of the studies having under-reported late term secondary malignancy should be considered.

This review does have a number of limitiations. First, all studies were retrospective and observational in design. To date, no prospective trials have been carried out assessing the benefit of adjuvant radiotherapy in managing recurrent pleomorphic adenoma. Retrospective observational studies are at a higher risk of bias than their prospective experimental counterparts [32], and significant selection bias was noted among the included studies. Participants in the adjuvant radiotherapy group were more likely to have a number of adverse prognostic factors and only one study [10] attempted to control for confounding factors.

Second, significant heterogeneity existed between the studies, particularly in terms of the surgical intervention performed. Four studies [12, 18, 19, 22] did not differentiate between enuclation and extracapsular dissection-despite significantly different recurrence rates between the two [15]. Likewise, there was variation in the methods used for administration of radiotherapy, with half of the studies [12, 17–19] failing to provide details on the type used. There was significant heterogeneity within the remainder, with two noting change in the method used during the course of their studies due to changes in standard practices.

Finally, the available studies have taken place over a prolonged period of time with dates ranging from 1952 to 2013. Standard practice for initial treatment of these neoplasms has changed over time, and the type of initial surgery is known to affect recurrence [6]. In the first half of the twentieth century, extracapsular enucleation was common practice. In the 1940s and 1950s, high recurrence rates were noted and in 1947, the technique of superficial parotidectomy was described [6, 33]. Gradually, this replaced enucleation as

the gold standard and recurrence rates dropped to between 2 and 5% [6].

To minimise the impact of this change in treatment on our results, we included only studies published within the last 30 years. However, given that these are retrospective studies, cover a lengthy data collection period, and recurrence may occur after a prolonged interval, enucleation was still reported as common practice for initial treatment in three studies [10, 17, 23]. This may falsely inflate recurrence rates when compared with current practice.

Despite these limitations, this study provides important information regarding the role of radiotherapy in the treatment of recurrent pleomorphic adenoma. Overall, the available evidence suggests that adjuvant radiotherapy is of benefit in reducing recurrence rates in patients with recurrent pleomorphic adenoma and certain adverse prognostic factors. While it appears not to have significant adverse effects, either on facial nerve function, or rate of secondary malignancy, high quality, prospective studies are lacking. We recommend careful use in patients at high risk of further recurrence and further research in the form of well-designed randomised controlled trials.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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