

Review Article

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Superficial versus total parotidectomy for metastatic cutaneous squamous cell carcinoma and melanoma of the head and neck: a systematic review

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Abstract

Objective. The extent of parotidectomy in the management of regional metastatic disease is controversial. This systematic review aimed to appraise data from studies evaluating superficial and total parotidectomy in metastatic cutaneous squamous cell carcinoma and cutaneous malignant melanoma of the head and neck.

Method. A systematic search of PubMed, Embase and Cochrane Library was performed. The protocol was registered with Prospero (CRD42020217962).

Results. A total of five studies evaluated cutaneous malignant melanoma. Only one compared outcomes of superficial and total parotidectomy: they found higher parotid area recurrence following superficial parotidectomy. Seven studies reported outcomes following cutaneous squamous cell carcinoma; some studies found higher regional recurrence and reduced survival in total parotidectomy, but there was likely selection bias in these studies. Others found no difference in survival between superficial and total parotidectomy.

Conclusion. The effect of the extent of parotidectomy on outcomes is unclear in cutaneous malignant melanoma and cutaneous squamous cell carcinoma. This systematic review highlights the need for well-designed studies to direct better care.

Introduction

Cutaneous squamous cell carcinoma is a common type of skin cancer, with reported age-standardised rates of 77.3 and 34.1 per 100 000 person years for males and females, respectively, in the UK.¹ There has been a steady increase in cutaneous malignant melanoma over the past decades. In the UK between 2016 and 2018, the average annual incidence rates of cutaneous malignant melanoma in females and males were 24.7 and 25.3 per 100 000 people, respectively.²

Metastatic cutaneous SCC and cutaneous malignant melanoma can spread regionally to involve adjacent parotid lymph nodes or cervical lymph nodes and to distant sites. Lymph nodes are present in both the superficial lobe and deep lobe below the facial nerve.^{1,3,4} Pisani *et al.* examined lymph nodes in 18 total parotidectomy specimens. They found that 21 per cent of lymph nodes were in the deep lobe.⁴ Studies evaluating parotid metastases from head and neck cutaneous SCC and cutaneous malignant melanoma found involvement of nodes that were both superficial and deep to the facial nerve.^{5,6}

The surgical management of the parotid gland by superficial parotidectomy or total parotidectomy in metastatic head and neck cutaneous SCC and cutaneous malignant melanoma is controversial. Some advise consideration of total parotidectomy in patients with evidence of superficial lobe metastases.^{6,7} However, total parotidectomy may increase the risk of surgically related morbidity, most notably for facial nerve function with limited improvement in parotid area recurrence and survival.^{8–11}

The UK head and neck guidelines on metastatic head and neck cutaneous SCC advise resection of involved parotid tissue in case of parotid-positive disease, without specific mention of the extent of parotidectomy.¹² The guidelines also recommend consideration of ipsilateral parotidectomy in parotid-negative disease with cervical involvement if the draining basin of the primary site is likely to pass through the parotid gland.¹² Similar recommendations were given for head and neck metastatic melanoma.⁵

The evidence to support the surgical management of the parotid gland for metastatic cutaneous malignant melanoma and cutaneous SCC of the head and neck is limited, particularly in regard to parotid gland management in patients with cervical nodal involvement without parotid involvement and the extent of parotidectomy in patients with only superficial parotid nodal involvement.

This systematic review aimed to appraise data from studies evaluating parotidectomy in metastatic cutaneous malignant melanoma and cutaneous SCC of the head and neck. The

primary objectives were to examine parotid area recurrence, morbidity and survival in those undergoing superficial parotidectomy and total parotidectomy.

Materials and methods

The systematic review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') guidelines. The protocol was registered with Prospero (CRD42020217962).

Eligibility criteria

Primary interventional or observational studies evaluating parotidectomy in metastatic cutaneous SCC or cutaneous malignant melanoma of the head and neck were included. There was no restriction on publication date. Articles that were not available in the English language, had fewer than 10 patients, and those that were case reports, commentaries or letters, review articles, or animal studies were excluded. The outcome measures evaluated included regional recurrence, distant recurrence, surgical morbidity, quality of life and survival.

Information sources

PubMed, Embase, Central, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were systematically reviewed.

Search strategy

The following search terms were used in all search fields: (parotidectomy) AND (melanoma OR squamous cell carcinoma OR SCC OR squamous).

Study records

Two authors (WSL, OE) independently screened titles and abstracts from the initial search. The full text of records considered relevant were retrieved for further eligibility assessment. The reference list of included articles was screened and relevant full texts were assessed. All data collected by one author were checked for accuracy by another author. The data were collected using a standard data collection proforma.

Data items

The following data were extracted from the manuscript: study characteristics (study type, year, country); participant characteristics (age, gender); parotid involvement of SSC or malignant melanoma; type of intervention (superficial or total parotidectomy, adjuvant radiotherapy or systemic therapy); and outcome measures (including local recurrence, survival, morbidity, quality of life). Superficial parotidectomy was defined as removal of parotid tissue superficial to the facial nerve. Total parotidectomy was defined as removal of all parotid tissue superficial and deep to the facial nerve.

Risk of bias in individual studies

Quality assessment was performed on included studies. A quality assessment tool developed by Murad *et al.* was used to assess case series or single arm studies.¹³

Data synthesis

A formal narrative synthesis was performed given the variability in extent of parotidectomy, neck dissection and use of adjuvant radiotherapy or chemotherapy. We described recurrence, complications and survival in individual studies and explored relationship in study design, outcomes and complication rates between studies.

Results

Figure 1 is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram that outlines the process of inclusion and exclusion of studies. In total, 12 studies were included in this systematic review.

Malignant melanoma

A total of 5 studies reported outcomes by extent of parotidectomy in metastatic cutaneous malignant melanoma (a total of 193 patients underwent superficial parotidectomy and 57 underwent total parotidectomy).^{6,7,14–16} See Table 1 for individual study outcomes.

Superficial parotidectomy

Superficial parotidectomy was performed in cases where there was no pre-operative evidence of parotid nodal involvement (electively)¹⁴ or as a therapeutic procedure with pre-operative evidence of parotid involvement.¹⁶

Berger *et al.* evaluated elective superficial parotidectomy in 40 patients with metastatic cutaneous malignant melanoma.¹⁴ No patient had pre-operative evidence of parotid involvement of disease. All patients had cervical lymph node involvement and also underwent concomitant neck dissection. In their series, 73 per cent had post-operative radiotherapy. A total of 25 of 40 patients (62.5 per cent) had recurrence: local (5 per cent), regional (3 per cent) and distant (55 per cent). Post-operative histology identified 10 of 40 (25 per cent) with occult positive parotid nodes. Of these, 8 patients (80 per cent) developed recurrence (compared with 17 of 30 (56 per cent) who did not have positive parotid nodes on histology). Two patients (5 per cent) in this series developed permanent facial weakness affecting the temporal or buccal branch. The median disease-specific survival for the cohort was 2.1 years.¹⁴

Another study evaluated superficial parotidectomy as an elective ($n = 16$) or therapeutic ($n = 30$) procedure in patients with metastatic cutaneous malignant melanoma.¹⁶ All patients had concomitant neck dissection. The authors did not report on the proportion of patients who underwent adjuvant treatment. Of the 16 patients who underwent elective superficial parotidectomy, 5 (31 per cent) had occult metastasis in the parotid lymph node. None of the patients had parotid area recurrence over a follow-up period of 4–19 years. The overall 5-year survival was 37 per cent.¹⁶

Martins *et al.* examined 12 patients with metastatic or adjacent parotid cutaneous malignant melanoma.¹⁵ Six patients (50 per cent) had clinically positive parotid nodes or neck nodes. All patients underwent superficial parotidectomy and neck dissection. There was no information provided on adjuvant treatments. They reported 1 case of locoregional recurrence (unclear from the reporting if this was parotid area or cervical), distant metastases in 50 per cent, and 25 per cent of patients had no evidence of disease at 27 months.¹⁵

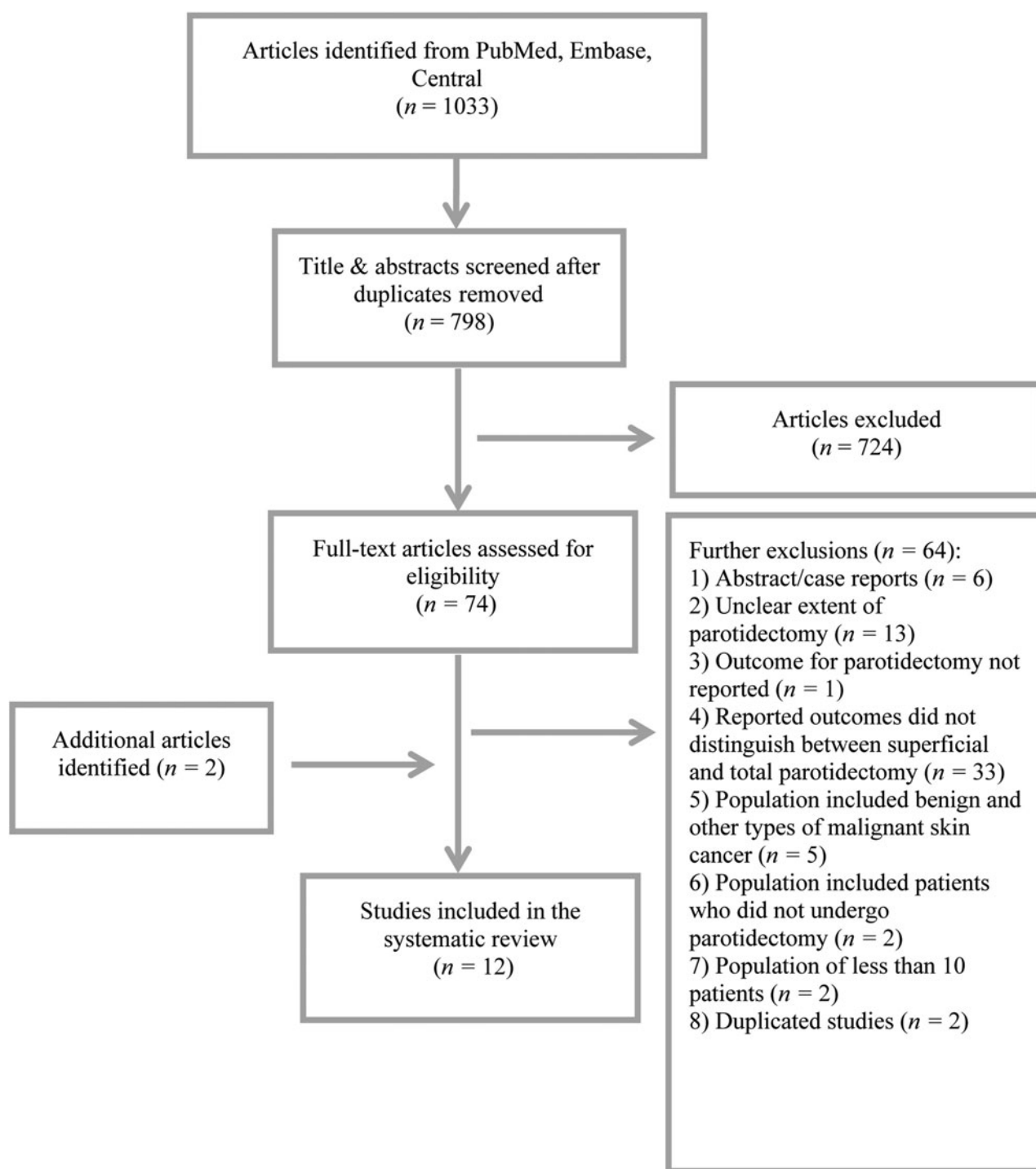


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses ('PRISMA') flow diagram showing study selection.

Total parotidectomy

Thom *et al.* evaluated the role of total parotidectomy and neck dissection in 23 patients with metastatic cutaneous malignant melanoma.⁶ All patients had nodal disease involving the superficial parotid. A total of 14 patients (61 per cent) had adjuvant radiotherapy ($n = 12$) or chemotherapy ($n = 2$). Three patients (13 per cent) had separate metastases to both the superficial and deep lobe on post-operative histology. The facial nerve was preserved in 21 patients (91 per cent) following total parotidectomy. No patient developed parotid area recurrence during a median follow up of 30.6 months; however, 6 patients (26 per cent) developed cervical recurrence and 11 patients (48 per cent) had distant metastases. All

3 patients with deep lobe involvement developed recurrence in the neck within 10 months of surgery.⁶

Superficial and total parotidectomy

One study compared the rate of parotid recurrence in patients who had undergone superficial parotidectomy or total parotidectomy for metastatic cutaneous malignant melanoma.⁷ They included a total of 129 patients; 34 underwent total parotidectomy and 95 had superficial parotidectomy. All patients had metastasis to the superficial parotid gland. There was no standardised protocol for the extent of parotidectomy. The indication for total parotidectomy was based on individual

Table 1. Characteristics of studies reporting on superficial parotidectomy and total parotidectomy in patients with cutaneous malignant melanoma

Study/year/country	Extent of parotidectomy	Duration of follow up	Outcomes	Morbidity
Superficial parotidectomy				
– Berger <i>et al.</i> , 2019, ¹⁴ Netherlands, <i>n</i> = 40	SP	2.2–7.1 years	Parotid area recurrence, 5%; neck recurrence, 2.5%; distant, 55% Disease-specific survival, 2.1 years	Facial weakness: 20% temporary, 5% permanent
– Martins <i>et al.</i> , 2000, ¹⁵ Brazil, <i>n</i> = 12	SP	Average, 27.4 months	Locoregional recurrence, 8% Distant metastases, 50% Survival, 25% at 27.4 months	
– Vaglini <i>et al.</i> , 1990, ¹⁶ Italy, <i>n</i> = 46	SP	4–19 years (average, 7.3 years)	Parotid area recurrence, 0% Overall survival, 37% at 5 years	Facial weakness: 28%
Total parotidectomy				
– Thom <i>et al.</i> , 2014, ⁶ USA, <i>n</i> = 23	TP	Median, 30.6 months	Parotid area recurrence, 0% Neck recurrence, 26% Distant metastases, 48%	Facial weakness: median HB grade of 3 improved to HB grade 1 after 1 year
Superficial & total parotidectomy				
– Wertz <i>et al.</i> , 2017, ⁷ USA, <i>n</i> = 129	SP = 95	Average, 24 months	Parotid area recurrence, 13%	Facial weakness: HB grade 1–3, 97%; HB grade 4–6: 3% Morbidity: 3% seroma/haematoma, 1% delayed wound healing
	TP = 34	Average, 16 months	Parotid area recurrence, 0%	Facial weakness: HB grade 1–3, 88%; HB grade 4–6, 9% Morbidity: 3% delayed wound healing

SP = superficial parotidectomy; TP = total parotidectomy; HB = House–Brackmann

surgeon's discretion; however, it was generally performed when there was pre-operative or intra-operative evidence of deep lobe involvement. Therefore, the outcomes of superficial parotidectomy and total parotidectomy are not directly comparable given the selection bias. The use of adjuvant treatment was similar in both groups. There was no difference in facial nerve function post-operatively. Superficial parotidectomy was associated with a significantly higher rate of parotid bed recurrence compared with total parotidectomy (13 per cent vs 0 per cent).⁷

Squamous cell carcinoma

In the studies that evaluated cutaneous SCC (*n* = 8), 326 patients underwent superficial parotidectomy, and 220 patients underwent total parotidectomy (Table 2).^{6,17–23}

Total parotidectomy

Thom *et al.* evaluated the outcomes of therapeutic total parotidectomy and ipsilateral neck dissection in 42 patients with metastatic cutaneous SCC.⁶ They found that 31 (74 per cent) patients had metastasis that involved the superficial lobe only and 11 (26 per cent) patients had metastasis that involved both superficial and deep lobes. A total of 9 patients (21 per cent) had adjuvant chemoradiotherapy and 27 patients (64 per cent) had radiotherapy alone. Patients were followed up for a median of 36.4 months: 3 (7 per cent) developed parotid area recurrence, 2 (5 per cent) had cervical recurrence and 9 (21 per cent) had distant metastases. There was no difference in 5-year locoregional control rates between patients without (88 per cent) and those with (78 per cent) deep parotid lobe involvement. In their univariate analysis, neck metastasis and

N₂ disease was associated with spread to deep parotid nodes. Involvement of the deep lobe of the parotid was associated with significantly higher rates of distant metastases, disease recurrence, death from disease and death from all causes.⁶

Superficial and total parotidectomy

The indication for superficial parotidectomy was metastatic cutaneous SCC to the parotid gland in the absence of clinical, radiological or intra-operative evidence of deep lobe involvement,¹⁹ or patients with cervical lymph node involvement with a primary tumour within the area of drainage of the parotid gland.²⁰

The following indications for total parotidectomy were reported: evidence of metastasis to deep parotid nodes,⁶ facial nerve involvement during pre-operative assessment or identification of deep lobe involvement intra-operatively.¹⁸ Seven studies reported outcomes of superficial parotidectomy and total parotidectomy in patients with metastatic head and neck cutaneous SCC (Table 2).^{17–23}

Hirshoren *et al.* reported outcomes in patients with metastatic cutaneous SCC who had superficial parotidectomy (*n* = 65) and total parotidectomy (*n* = 13).¹⁹ The indication for superficial parotidectomy was metastatic cutaneous SCC to the parotid in the absence of clinical, radiological or intra-operative evidence of deep lobe involvement (otherwise a total parotidectomy was performed).²² All patients had parotid lymph node involvement at presentation. A neck dissection was performed on 62 per cent (40 of 65) of patients who had superficial parotidectomy and 46 per cent (6 of 13) of patients who had total parotidectomy. Patients were followed up for a minimum of five years. Regional recurrence was observed in 11 patients (17 per cent) who underwent

Table 2. Characteristics of studies reporting on superficial parotidectomy and total parotidectomy in patients with cutaneous squamous cell carcinoma

Study	Extent of parotidectomy	Duration of follow up	Outcomes	Morbidity
Total parotidectomy				
– Thom <i>et al.</i> , 2014, ⁷ USA, <i>n</i> = 42	TP	Median, 36.4 years	Parotid area recurrence, 7%; regional, 5%; distant recurrence, 21%	Facial weakness: median HB grade 3 improved to HB grade 1 after 1 year
Superficial & total parotidectomy				
– Cassisi <i>et al.</i> , 1978, ¹⁷ USA, <i>n</i> = 15	SP = 13	18–74 months	Parotid area recurrence, 38% Survival, 62%	
	TP = 2		Parotid area recurrence, 0% Survival, 50%	
– Goh <i>et al.</i> , 2012, ¹⁸ Australia, <i>n</i> = 67	SP = 53	2–5 years	Disease-specific survival, 17% at 10 years	
	TP = 14		Disease-specific survival, 0% at 10 years	
– Hirshoren <i>et al.</i> , 2018, ¹⁹ Australia, <i>n</i> = 78	SP = 65	5 years	Regional recurrence, 17% Five-year regional control rate, 73% Five-year overall survival, 45%	
	TP = 13		Regional recurrence, 31%	Facial weakness: 31% (intentionally sacrificed)
– Kempel <i>et al.</i> , 2021, ²⁰ Israel, <i>n</i> = 67	SP = 27	3 months to 5 years	8 patients had treatment failure, 3 died within 3 months post-operation, & 4 died within 1 year across all treatment modalities	
	TP = 20			
– Moore <i>et al.</i> , 2005, ²¹ USA, <i>n</i> = 193	SP = 41		Extent of parotidectomy performed & facial nerve sacrifice did not significantly affect any survival outcome or time to recurrence	
	TP = 17			
– Sweeney <i>et al.</i> , 2014, ²² USA, <i>n</i> = 218	SP = 110	N/A	Overall survival not affected by extent of parotidectomy	
	TP = 108			
– Xie <i>et al.</i> , 2020, ^{23*} China, <i>n</i> = 21	SP = 17	11–138 months	Parotid area recurrence, 29% Overall survival, 24% died	
	TP = 4		Parotid area recurrence, 0% Overall survival, 75% died	

*External auditory canal squamous cell carcinoma. TP = total parotidectomy; SP = superficial parotidectomy; SCC = Squamous cell carcinoma; HB = House-Brackmann

superficial parotidectomy and 4 patients (31 per cent) who underwent total parotidectomy.¹⁹

Moore *et al.* also evaluated the outcomes in 40 patients with metastatic head and neck cutaneous SCC.²¹ All patients had evidence of metastatic disease involving the parotid gland, cervical nodes or both at presentation; of these patients, 22 underwent superficial parotidectomy and 9 underwent total parotidectomy. The indication for extent of parotidectomy was not reported. A total of 26 patients (65 per cent) had concomitant neck dissection, and 37 patients (92.5 per cent) underwent post-operative radiotherapy. The authors reported that the extent of parotidectomy and facial nerve sacrifice did not significantly affect any survival outcome or time to recurrence.²¹

Goh *et al.* evaluated 67 patients with metastatic cutaneous SCC who underwent superficial parotidectomy (*n* = 53) and total parotidectomy (*n* = 14); of these patients, 41 patients (61 per cent) presented with parotid node metastasis and 26 patients (39 per cent) presented with both parotid and cervical lymph node metastasis.¹⁸ The indication of total parotidectomy was pre-operative or intra-operative facial nerve involvement. A total of 54 patients (81 per cent) had concomitant ipsilateral neck dissection. All patients had adjuvant

radiotherapy, and three patients had additional chemotherapy. Follow up ranged between 2 and 5 years. Patients who underwent superficial parotidectomy had a 10-year disease-specific survival of 17 per cent (8 of 47) compared with 0 per cent (0 of 14) for patients who underwent total parotidectomy.¹⁸

Kempel *et al.* evaluated 67 patients with advanced cutaneous SCC who underwent superficial parotidectomy (*n* = 27), total parotidectomy (*n* = 20), neck dissection (*n* = 14) and excision of primary tumour only (*n* = 6).²⁰ A total of 35 patients (52 per cent) had parotid involvement at presentation and subsequently underwent parotidectomy, including superficial parotidectomy (*n* = 19) and total parotidectomy (*n* = 16). The extent of parotidectomy was at individual surgeon's discretion. There was no difference in survival between total parotidectomy or radical parotidectomy compared with superficial parotidectomy. However, comparisons between parotidectomy and no parotidectomy showed improved overall 5-year survival in patients who underwent parotidectomy (59 per cent vs 18 per cent).²⁰ However, this was not statistically significant in multivariable analysis.

Sweeney *et al.* evaluated 218 patients who underwent superficial parotidectomy (*n* = 110) and total parotidectomy

Table 3. Quality assessment of included studies

Study	Patient representation	Exposure ascertained	Outcome ascertained	Alternative causes influence outcome	Replicability	Score*
Berger <i>et al.</i> , 2019 ¹⁴	Yes	Yes	Yes	No	Yes	4
Martins <i>et al.</i> , 2000 ¹⁵	Yes	Yes	Yes	No	No	3
Vaglini <i>et al.</i> , 1990 ¹⁶	Yes	Yes	Yes	No	No	3
Thom <i>et al.</i> , 2014 ⁶	Yes	Yes	Yes	No	No	3
Wertz <i>et al.</i> , 2017 ⁷	Yes	Yes	Yes	No	No	3
Cassisi <i>et al.</i> , 1978 ¹⁷	No	Yes	No	No	No	1
Goh <i>et al.</i> , 2012 ¹⁸	Yes	Yes	No	No	Yes	3
Hirshoren <i>et al.</i> , 2018 ¹⁹	Yes	Yes	No	No	Yes	3
Kampel <i>et al.</i> , 2021 ²⁰	Yes	Yes	No	No	No	2
Moore <i>et al.</i> , 2005 ²¹	Yes	Yes	No	No	Yes	3
Sweeny <i>et al.</i> , 2014 ²²	Yes	Yes	No	No	No	2
Xie <i>et al.</i> , 2020 ²³	No	Yes	No	No	No	1

*Maximum score = 5

($n = 108$) for metastatic cutaneous SCC.²² The indication for extent of parotidectomy was not reported; 81 per cent had concomitant neck dissection, and 48 per cent had adjuvant radiotherapy. Survival was not affected by the extent of parotidectomy and was similar irrespective of parotid lymph node involvement. However, overall survival decreased when cervical node involvement was present.²²

Two studies with very small cohorts ($n = 15$ and 21) also reported outcomes by extent of parotidectomy in patients with head and neck cutaneous SCC with parotid area involvement (see Table 2).^{17,23} Table 3 shows the quality assessment of the included studies. The median quality score was 3 out of 5.

Discussion

This systematic review reported outcomes in patients with metastatic cutaneous SCC and cutaneous malignant melanoma who underwent parotidectomy as part of their surgical management.

Only five studies reported the outcomes of the extent of parotidectomy in patients with cutaneous malignant melanoma. The effect of parotidectomy was generally a secondary objective. In addition, four of these studies had no control group. Only one study directly compared outcomes between superficial parotidectomy and total parotidectomy in patients with metastatic cutaneous malignant melanoma.⁷ The authors found a significantly higher rate of parotid area recurrence in patients who had superficial parotidectomy compared with total parotidectomy; there was no difference in post-operative facial function.⁷ However, their analysis is limited by selection bias as the choice of extent of surgery was at the surgeons' discretion and influenced by tumour characteristics.

The outcomes following superficial parotidectomy and total parotidectomy for cutaneous SCC were reported in seven studies. There are conflicting findings: some found higher regional recurrence¹⁹ and reduced survival in total parotidectomy.^{18,23} Other authors found no difference in survival between superficial parotidectomy and total parotidectomy.²⁰ Two studies reported that the survival outcomes were not affected by the extent of parotidectomy; however, there were no specific data or survival analyses available to support these conclusions.^{21,22}

A possible explanation for the fact there was no difference between superficial parotidectomy and total parotidectomy is that most patients have adjuvant radiotherapy. This may treat occult metastases in the deep lobe in patients who undergo superficial parotidectomy. Comparisons of outcomes were limited by the small sample sizes and selection biases.

Some authors recommend total parotidectomy in cutaneous malignant melanoma with nodal metastases in the parotid gland, even if considered to be only affecting nodes superficial to the facial nerve.⁶ The rationale is to clear all parotid lymph nodes and reduce regional recurrence rates from occult positive deep lobe disease. In the case of a positive cervical node without parotid involvement, the rationale is to clear a possible occult node in the parotid gland: if the primary cutaneous disease is at a site thought to drain through the parotid gland (i.e. the scalp, forehead and lateral aspect of face (temple, cheek, periauricular)).²⁴ In the setting of metastatic cutaneous malignant melanoma, one argument for total parotidectomy would be the high rate (13 per cent) of occult nodal disease reported in the deep lobe.⁶

The difference in morbidity between superficial parotidectomy and total parotidectomy is important for decision-making. Although most small series report no difference between superficial parotidectomy and total parotidectomy with regards to facial weakness in our review,^{21,22} systematic reviews have found higher rates of paresis of 6.75 per cent and 15 per cent in superficial parotidectomy and total parotidectomy, respectively, for benign tumours. Furthermore, the mean rate of facial paralysis was 0.8 per cent and 4.4 per cent after superficial parotidectomy and total parotidectomy, respectively.²⁵

There are a number of limitations to this systematic review. Generally, the extent of parotidectomy (superficial vs total) was not comparable because the extent of parotidectomy was often based on the pre-operative extent of disease; therefore, it was limited by selection bias. In addition, the heterogeneity in practices and study methods prevented quantitative summation and analysis.

Based on the findings of this systematic review, there is a scope for a well-designed multicentre study with a prespecified treatment protocol, which can address the following controversies: superficial parotidectomy or total parotidectomy or active

monitoring of the parotid area for patients with head and neck cutaneous SCC or cutaneous malignant melanoma with no clinical evidence of parotid node involvement but with cervical involvement, and superficial parotidectomy or total parotidectomy in patients with head and neck cutaneous SCC or cutaneous malignant melanoma with pre-operative evidence of superficial parotid nodal involvement. This would help identify the relationship between the extent of parotidectomy against functional and oncological outcomes. Variables such as tumour stage, neck dissection and adjuvant treatment would also need to be controlled.

Conclusion

The association between extent of parotidectomy and outcomes in cutaneous malignant melanoma and cutaneous SCC remains unknown because of lack of data, varied practices, selection biases and small sample sizes. This systematic review highlights the need for well-designed studies to direct better care.

Competing interests. None declared

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