Systematic Review

Impact of adjuvant therapy on survival in patients with myoepithelial carcinoma: A systematic review and individual patient data analysis of 691 patients

Prashanth Giridhar [a], Pooja Gupta [a], Supriya Mallick [a,*], Ashish Dutt Upadhyay [b], Goura K. Rath [a]

[a] Department of Radiation Oncology; and [b] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Introduction: Myoepithelial carcinoma (MEC) is an extremely rare low grade salivary gland neoplasm [1–4]. A surgical resection is considered as corner stone of therapy. Role of adjuvant therapy is not clear.
Methodology: We performed systematic review and individual patient data analysis of 691 patients to look into the impact of adjuvant therapy and different prognostic variable for MEC.
Results: Data of 691 individual patients were retrieved from 340 publications. Median age of presentation was 56 years (Range: 0–103 years) with a trend of increasing incidence for increase in age. Major salivary glands (36.4%) were the commonest sub-site followed by minor salivary glands, skin and soft tissue, and breast. Median PFS and OS of entire cohort was 48 months (95% CI: 30–65 months) and 167 months (95% CI: 82–251 months). In univariate analysis A R0 resection was associated with significantly better PFS and OS. Median PFS and OS were significantly worse for patients with tumour size >5 cm compared to smaller tumours and for patients with a mitotic index >10/10 high power field (hpf) compared to lower mitotic index. Adjuvant radiation was found to reduce loco-regional recurrence. Adjuvant radiation and chemotherapy both were associated with negative impact on survival in univariate analysis. This negative impact on survival was lost in multivariate analysis.
Conclusion: MEC appears to be a low grade malignancy with good survival outcome. A R0 resection should be the standard of care. Adjuvant radiation should be considered for patients with adverse risk features to improve loco-regional disease control.

© 2019 Elsevier B.V. All rights reserved. Radiotherapy and Oncology 140 (2019) 125–130

Myoepithelial carcinoma (MEC) is an extremely rare salivary gland malignancy accounting for 1% of all salivary gland cancers [1–4]. MEC has long been reported as a low grade malignancy with indolent clinical behaviour and good long-term survival [5]. These tumours have been reported to arise from a number of organs viz. major and minor salivary gland, breast, airway, etc [1,6,7]. Irrespective of sub-site, surgical resection is considered as corner stone of therapy. Even after surgical resection recurrence has been reported, and this highlights an aggressive group of MEC and a plausible benefit of adjuvant therapy. Owing to rarity only a handful of cases have been reported so far which precludes drawing firm conclusion about the demography, natural history, patterns of care of such patients. In addition, it is difficult to understand the benefit of adjuvant radiation or chemotherapy on patterns of recurrence and survival. A prospective study also appears far from practical for this rare disease, which led us to embark upon doing a systematic review and individual patient data analysis of all such published cases. We wanted to look into the demography and pattern of care of MEC. In addition, we aimed to address two questions "does adjuvant radiation decrease loco-regional recurrence and improve survival outcome for MEC?" and "what are the risk factors that affect survival in MEC?"

Search methodology

In order to retrieve all relevant publications of MEC we performed a comprehensive search of the PubMed, and Google scholar with the following Mesh terms: "Myoepithelial carcinoma; Malignant myoepithelioma; Myoepithelial tumour; Epithelial-myoepithelial carcinoma; Myoepithelial carcinoma AND radiotherapy; Myoepithelial carcinoma AND radiation; Epithelial-myoepithelial carcinoma AND radiotherapy". We restricted our search to English language only and all publications till 1st July 2018 were considered eligible. From the initial abstracts we excluded the unrelated ones and then attempts were made to access all full text articles and the corresponding authors were communicated to furnish full text if not available online. After

initial search we excluded publications of those that did not furnish demography and survival outcome and focused only on pathology and molecular assessment. The references of the relevant selected articles were then hand searched for additional articles. On completion of search following information were tabulated in the predesigned excel chart- location and size of primary, pathological information (Ki-67%, mitotic index, Tumour size and p63 positivity) surgery, type of surgery [R0 vs. R1/2], adjuvant treatment received, duration of Progression free survival, overall survival, site of recurrence and salvage treatment. The data were later verified independently by two individual authors and possible duplications were removed. The PRISMA chart (Fig. 1) explains the data synthesis from the eligible studies.

Statistical analysis

Data were analysed and categorical variables were summarized by frequency and percentage and quantitative variables by the median and range. We defined events as progression free survival (PFS) and overall survival (OS) which were calculated from the date of diagnosis to the date of documented progression and death respectively. Chi square test was used to identify selection bias of candidates for different variables. For survival analysis Kaplan–Meier's method was used and a p value of <0.05 was taken as significant. Uni-variate analysis using log rank test was done to find the impact of age, gender, location, pathological features, surgery, use of radiation and chemotherapy on survival outcomes. Significant co-variates were then subjected to multi-variate analysis by Cox regression statistics. SPSS v21 was used for all statistical analysis.

Results

Patient characteristics

Data of 691 patients of MEC was retrieved from 340 publications till July 2018. MEC was found to affect females more commonly with a male to female ratio being 1: 1.21. Median age of presentation was 56 years (Range: 0–103 years). With increasing age, incidence of MEC showed a rise in all sub-sites except for skin and soft tissue primary. In skin and soft tissues, the peak incidence is in first two decades of life followed by a sharp fall [Fig. 2]. One third patients were found to have the primary from the major salivary glands (36.4%; $n = 253$) followed by minor salivary glands (15.7%; $n = 109$), skin and soft tissue (11.0%; $n = 77$) and breast (8.6%; $n = 60$). Median tumour size was 3.5 cm (Range = 0.5–80 cm) and 28 % patients had tumours of >5 cm. Interestingly, 35 (5%) patients had palpable regional nodes at presentation and 2% patients had distant metastasis at presentation.

Treatment characteristics

Information regarding surgery was available in 596 patients. Surgery was attempted in 574 (96%) patients. 22 (4%) patients did not undergo surgery. Information on extent of surgery was available for 169 patients. R0 resection was achieved in 127 (75%) and R1 resection was achieved in 42 (25%) patients. Information regarding whether radiotherapy was part of treatment was documented in 505 patients. Radiotherapy was part of treatment in 163 (32%) patients. Pre-operative radiotherapy was delivered in 3 patients whereas definitive radiotherapy was delivered in 10 patients and
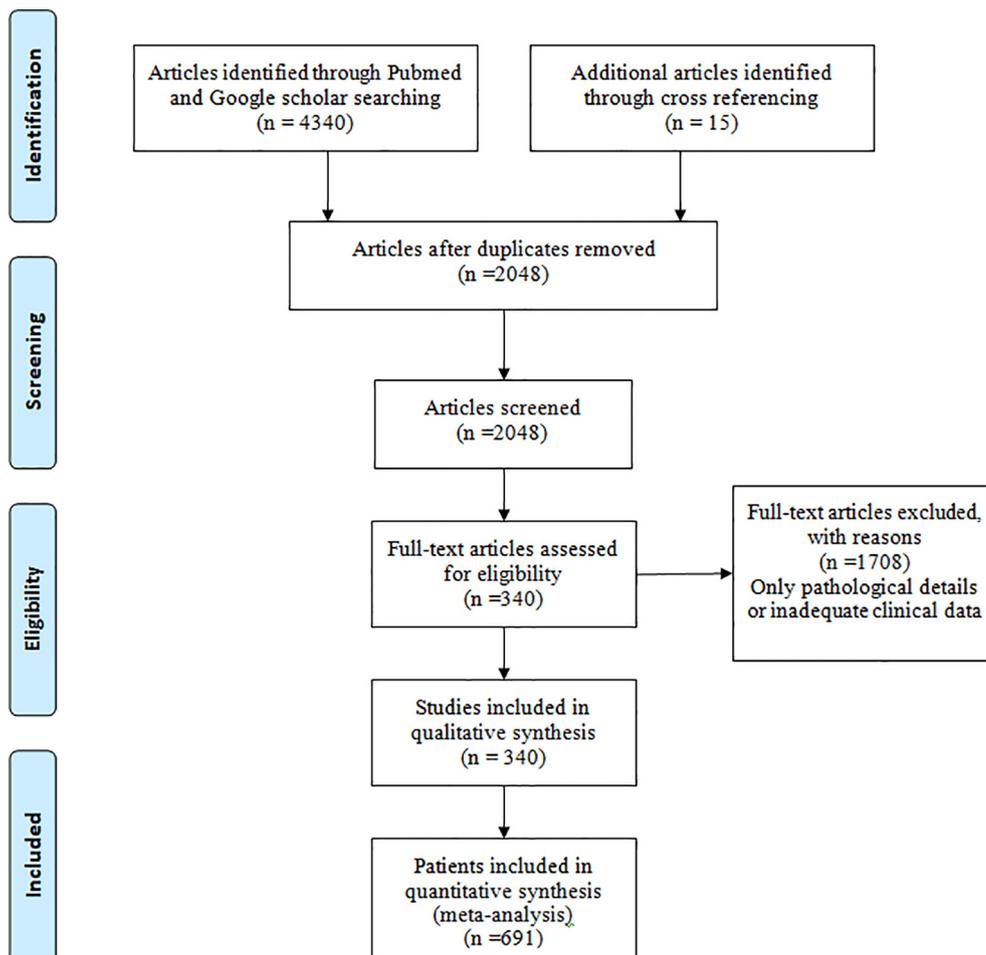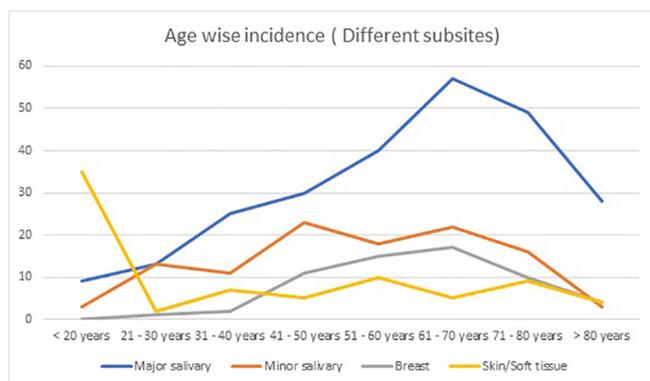

Fig. 1. PRISMA flow diagram showing selection of eligible publications for the systematic review.

Fig. 2. A line diagram showing the incidence in different age group for different subsites.

110 (21.8%) patients received adjuvant radiation. The intent of treatment was palliative in 4 patients. Information regarding sequencing of radiotherapy was not clearly documented in 36 patients. The median dose of post-operative radiation was 60 Gy (Range = 36–91.6 Gy). The median dose of definitive external beam radiation was 62 Gy (Range = 55–66 Gy). Chemotherapy was part of treatment in 81 (11%) patients. The intent of chemotherapy was clearly mentioned only in 33 patients (Adjuvant = 16 patients; Neoadjuvant = 11 patients; Palliative = 6 patients). The various chemotherapeutic agents used were Doxorubicin, Cisplatin, 5Fluoro-Uracil, Paclitaxel, Carboplatin, Ifosfamide, Etoposide, Docetaxel, TS1, Camptothecin analogues, Cyclophosphamide, Vincristine, Gemcitabine, Bevacizumab and isolated limb perfusion with Melphalan and Dactinomycin. Cisplatin alone or in combination with other agents was the most common drug used (n = 4). Patient demographic and treatment details are summarized in Table 1.

Survival analysis

Median PFS of entire cohort was 48 months (95% CI: 30–65 months). Median OS of entire cohort was 167 months (95% CI: 82–251 months).

Effect of surgery on survival

Patients with R0 resection compared to R1 resection had significantly better PFS [Median PFS: 120 months; 95% CI: 29–211 vs. 24 months; 95% CI: 0–78; p = 0.007] [Fig. 3A]. Patients with R0 resection had significantly better median OS compared to those with R1 resection [Median OS: 192 months; Standard error = 0.000 vs. 76 months; 95% CI: 18–134 months; p = 0.001] [Fig. 3B]. We analysed the distribution of prognostic factors and recurrence rates in patients for whom extent of surgery was documented. There was a numerically higher occurrence of R1 resection in patients with >5 cm size tumour (34% vs 22%; p = 0.225). There was also a difference in R1 resection rates based on location of primary with R1 resection rates of 48% in major salivary glands versus 24% and 7% for skin/soft tissue primary and minor salivary glands respectively (p = 0.004). There was no variation in incidence of R1 resection rates based on mitotic index (p = 1.000). There was significantly higher incidence of recurrence among patients who underwent R1 resection (p = 0.001). Due to low patient numbers (n = 10), no meaningful analysis of definitive radiotherapy versus surgery on PFS or OS could be done.

Effect of pathological features on survival

Effect of tumour size, Ki-67 values, mitotic index and p63 positivity on PFS and OS was analysed by log rank test. Median PFS

Table 1
Demographic and treatment features of myoepithelial carcinoma.

Demographic features	No. of patients (n)	Percentage (%)
Gender		
Males	311	45
Females	376	55
Sub-sites		
Major salivary glands	253	36.6
Minor salivary glands	109	15.8
Skin/Soft tissue	77	11.1
Breast	60	8.7
Nasal cavity/Nasopharynx	60	8.7
Airway below base of tongue	63	9.1
Others	66	9.5
Not clear	3	0.5
Tumour size		
<5 cm	318	72
>5 cm	121	28
Mitotic index		
<10/10 hpf	121	69.5
>10/10 hpf	53	30.5
Ki-67		
<30%	54	75
>30%	18	25
P63		
Positive	129	88
Negative	17	12
Extent of surgery		
R0 resection	127	75
R1 resection	42	25
Radiotherapy		
Radical	10	8
Post operative	110	92
Chemotherapy		
Yes	81	18.8
No	348	81.2

was significantly worse for patients with tumour size >5 cm compared to smaller tumours [Median PFS 36 months; 95% CI: 16–56 vs. 79 months; 95% CI: 39–119 months; p = 0.001] [Fig. 3C]. Median PFS was worse for patients with a mitotic index >10/10 high power field (hpf) compared to lower mitotic index [Median PFS: 36 months; 95% CI: 7–65 vs. Not reached) but did not reach statistical significance (p = 0.107 [Fig. 3D]. Median PFS varied widely across different sub-sites. Median PFS for primary major salivary gland tumour was 60 months [95% CI: 0.6–119.5 months] while it was 24 months for skin and soft tissue primary [95% CI: 13–35 months] and 31 months for breast primary [95% CI: 21–41 months] [Fig. 3E]. Median OS was significantly worse for patients with tumour size >5 cm compared to smaller tumours [Median OS: Not reached vs. 192 months; 95% CI: 89–295 months; p = 0.000] [Fig. 3F]. Median OS was worse for patients with a mitotic index >10/10 high power field (hpf) compared to lower mitotic index [Median OS: Not reached) (p = 0.016) [Fig. 3G]. Median OS also varied significantly according to location of primary (p = 0.001). Median OS was 192 months for major salivary gland primary (Standard error = 0.000); and 49 months for breast primary (95% CI: 30–68 months) [Fig. 3H]. Ki-67% and p63 positivity had no effect on PFS and OS.

Effect of radiotherapy on survival and patterns of recurrence

Due to lack of consensus and evidence, use of adjuvant radiotherapy was individualized in most case reports. We performed a chi square test to identify if selection bias of candidates for radiotherapy was present for the above identified prognostic factors of survival (Tumour size >5 cm, high mitotic index and R1 resection).
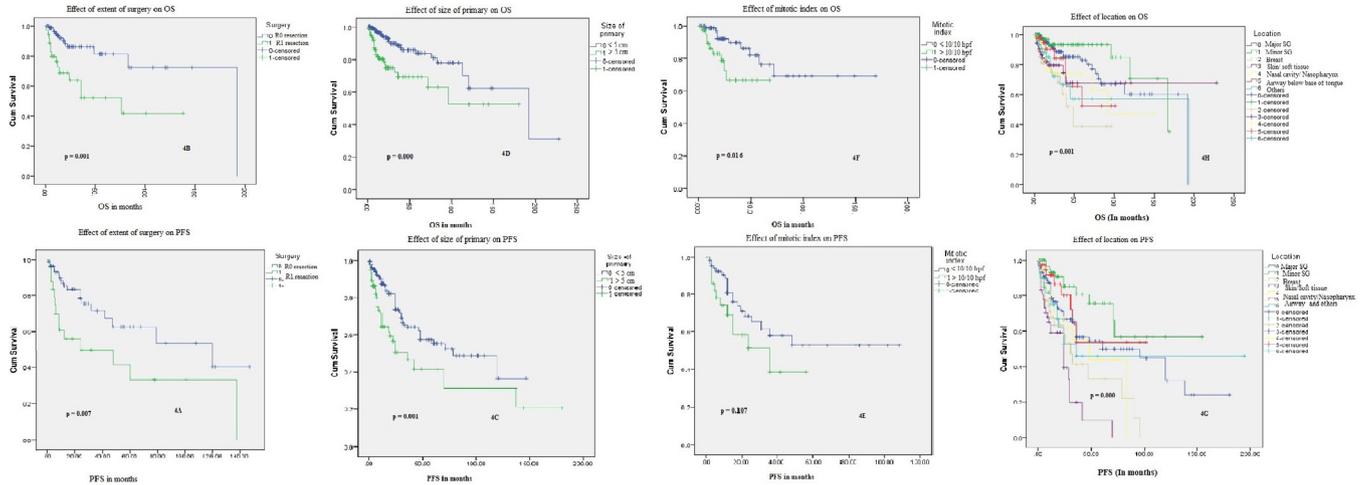
Fig. 3. Kaplan–Meier's graph depicting PFS and OS according to extent of surgery (A), (B); PFS according to the size of the primary tumour (C), mitotic count (D), location of tumour (E) and OS according size of the primary tumour (F), mitotic count (G), location of tumour (H) of all different subsites of tumour.

Significantly higher number of patients with the poor prognostic factors received radiotherapy (Table 2). We then analysed if adjuvant radiotherapy decreased loco-regional recurrence rates (LRR) versus metastases by Fischer's exact test. Adjuvant radiotherapy significantly decreased LRR ($p = 0.008$). Median PFS of patients of MEC who received radiotherapy (Median PFS = 36 months; 95% CI: 21–52 months) was not significantly different from patients who did not (Median PFS = 48 months; 95% CI: 19–77 months) ($p = 0.182$). The difference in patterns of recurrence (LRR versus distant) with adjuvant radiotherapy versus no radiotherapy is depicted in Fig. 4. Median OS of patients receiving radiotherapy was significantly worse (Median OS = 92 months; 95% CI: 65–119 months) than patients who did not receive radiotherapy (Median OS = 192 months; 95% CI: 91–293 months) on univariate analysis ($p = 0.04$). But, the apparent negative impact of radiotherapy on OS lost significance on multivariate Cox regression analysis ($p = 0.223$).

We also analysed the effect of adjuvant radiotherapy in patients who underwent R1 resection. Patients who underwent adjuvant radiotherapy had better PFS (Median PFS = 24 months; 95% CI: 0–89 months) in comparison to those who did not (Median PFS = 8 months; 95% CI: 0–58 months) ($p = 0.326$). There was no difference in OS between patients who underwent adjuvant radiotherapy versus those who did not (Median OS = 36 months for both groups; $p = 0.893$) in this cohort of patients.

Effect of chemotherapy on survival and patterns of recurrence

Significantly higher number of patients with tumour size >5 cm received chemotherapy but no significant selection bias was found

Table 2
Distribution of patients receiving adjuvant radiation (RT) as per identified prognostic factors.

Prognostic factor	Adjuvant RT not given	Adjuvant RT given	*p* value (Chi Square)
Tumour size			
<5 cm	176 (77%)	54 (23%)	0.006
>5 cm	61 (61%)	38 (38%)	
Mitotic index			
<10/10 hpf	76 (80%)	19 (20%)	0.101
>10/10 hpf	31 (68%)	15 (32%)	
Extent of surgery			
R0 resection	80 (70%)	34 (30%)	0.055
R1 resection	19 (53%)	17 (47%)	
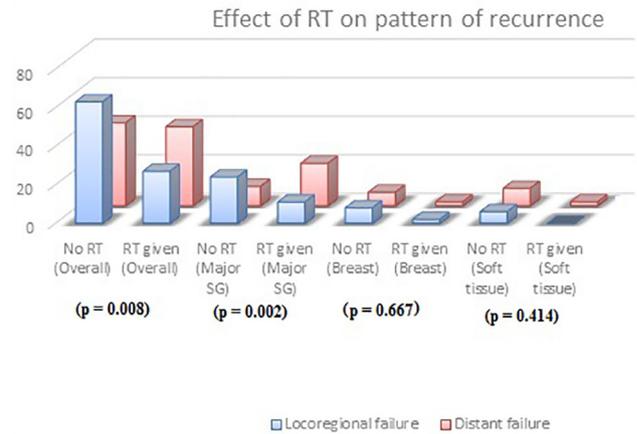
Fig. 4. Comparative bar diagram depicting loco-regional and systemic failure according to utilization of RT.

based on R1 resection and mitotic index. Administration of chemotherapy did not significantly decrease distant recurrence ($p = 0.509$) or LRR ($p = 0.066$) rates. Because of small sample size we could not perform meaningful survival analysis to look into the impact of chemotherapy.

Patterns of recurrence

A total of 214 (31%) patients had documented recurrence. Information regarding site of recurrence was available for 191 patients. Loco-regional recurrence occurred in 96 (44.8%) patients while distant recurrence occurred in 95 (44.4%) patients. Sites of distant recurrence were defined in 66 cases. Lung was the most common site of distant recurrence seen in 39 (59%) patients followed by soft tissue ($n = 11$) and bone ($n = 8$). Other sites of recurrence included brain ($n = 6$), liver ($n = 6$), kidney ($n = 3$), caecum ($n = 1$) and thyroid ($n = 1$). Patients who received adjuvant radiotherapy had more distant failure and less loco-regional failure and this pattern was observed across all sub-sites.

Discussion

MEC, is a rare malignant neoplasm arising from salivary tissue constituting nearly 1% of all salivary neoplasm [1–4]. The present

analysis, to our knowledge, is the largest single study as it represents data of 691 individual patients. The SEER database analysis published in 2010 could analyse 246 cases of salivary gland MEC over a period of 1973–2010. The earlier SEER analysis by Vazquez et al. [5] and the updated SEER analysis [8] reported slight female preponderance (57.3%) which closely corroborates our analysis highlighting a male:female ratio of 1:1.21. Major salivary glands were found to be affected most commonly followed by minor salivary gland and skin validating the finding of Seethala et al. [9]. In our analysis patients appear to be affected at a younger age (median age at diagnosis 56 years) compared to other published reports [5]. Interestingly, we observed a peak in incidence in sixth decade for major salivary gland tumour while in 2nd decade for tumour arising from skin and soft tissue. These young patients with MEC arising from skin and soft tissue are found to have lower PFS and OS and merit more aggressive treatment approach compared to salivary gland MECs. Contrary to the few previous publications reporting as high as 21% clinical nodal involvement [5] the present analysis found only 5% patients with clinical nodal involvement at presentation highlighting indolent clinical behaviour. This finding re-emphasizes the low rate of clinical nodal involvement reported in the SEER analysis [8].

In the absence of clear evidence, a curative surgery forms the cornerstone of therapy [5,8]. In the present analysis 96% patients underwent surgical resection. We aimed to look into the impact of extent of surgery. Patients who had a R0 resection had significantly favourable PFS and OS outcome compared to those with a R1 resection. Median PFS and OS were nearly 10 years and 16 years for patients with R0 resection compared to 2 and 6 years for patients with R1 resection emphasizing the impact of a curative surgical resection in these patients. This also points towards the fact that such patients should be dealt with great care in high volume centres with expertise in managing such rare cases. Even after curative surgical resection nearly one-third of the patients experience recurrence and nearly 14 % patients experience distant metastasis. A look into the possible prognostic factors highlighted poorer survival for patients with high mitotic index and tumour size exceeding 5 cm. High mitotic count was reported as an important prognostic factor for recurrence and metastasis adversely impacting survival [10]. Few of the other previously published adverse prognostic factors viz. Ki67 and p63 [10,11] positivity were not found to impact the survival outcome i.e. PFS or OS. Point should be made that these studies included small number of patients ($n = 16$) and the adverse impact could have been because of selection bias.

In the absence of level I evidence, surgery has long been considered the cornerstone of treatment for MEC. For a long time MEC has been considered a low grade neoplasm and the importance of adjuvant therapy either radiation or chemotherapy has not been properly elucidated. A few reports though have highlighted a favourable role of adjuvant radiation in reducing the rate of local recurrence [12,13] without much impact on survival outcome [5]. As Vazquez et al. reported comparable survival outcome for patients treated with surgery alone or with surgery followed by adjuvant radiation (93.2% vs. 87.6%, $p = 0.48$). We aimed to find the impact of adjuvant radiation on the outcome of MEC. In the absence of data, adjuvant radiation is advocated only for patients with incomplete resection and other high risk features. This is clearly evident as only a fifth of cases received adjuvant radiation in the present analysis. A chi square test performed to identify selection bias of candidates found that significantly higher number of patients with adverse prognostic factors i.e. tumour size >5 cm, high mitotic index and R1 resection had received adjuvant radiotherapy. On assessing the impact of radiation on loco-regional recurrence [LRR] by Fischer's exact test, we found that adjuvant radiation significantly decreased LRR ($p = 0.008$). But on analysing the impact of adjuvant radiotherapy on survival, it is seen that adjuvant radiotherapy does not significantly affect PFS but may be associated with a slightly worse OS. Looking at the pattern of recurrence, it is seen that patients receiving adjuvant radiotherapy fail more distally in comparison to loco-regional recurrence irrespective of sub-site. In light of selection bias of adjuvant radiotherapy towards poor prognostic factors, the question of use and impact of chemotherapy to take care of distant recurrence arises. Adjuvant radiotherapy therefore has to be considered in patients with poor prognostic factors i.e. large tumour size, R1 resection and high mitotic index to decrease risk of loco-regional recurrence while no recommendation for chemotherapy can be made. The impact of chemotherapy was difficult to assess as only 11% patients received chemotherapy with a widely variable regimen.

Median PFS and OS of entire cohort were 48 and 167 months which varied widely across different sub-sites. Survival outcome was favourable for salivary gland primary and unfavourable for breast primary and skin/soft tissue primary. Interestingly, the patients experience both loco-regional failure and distant metastasis. Therefore, regular follow-up with clinical examination, loco-regional imaging and systemic evaluation plays a crucial role. The most common site of distant failure was the lungs. Therefore a CECT thorax may be warranted during regular follow up.

Being a retrospective individual patient data analysis, the study has few limitations as well. The study results should be interpreted with caution as these are influenced by inherent bias of a retrospective analysis including publication bias. In addition, data were not available for all the individual cases and analysis was restricted to the available cases only. But performing a prospective study for such rare tumours is practically not feasible. In the absence of better quality data, an individual patient data analysis provides a higher level of evidence for patient care. We would also like to point out that case reports have been published from different parts of the world and should be considered representative of the disease burden, patterns of care and survival outcomes.

Conclusion

Myoepithelial carcinoma is a malignancy with favourable long-term survival. Its incidence increases with age except in soft tissues where its incidence peaks in the first two decades of life. A R0 resection should be the standard of care. Adjuvant radiotherapy significantly decreases loco-regional recurrence with no impact on survival and should be advocated in patients with adverse risk factors.

Financial support

No financial support received.

Declaration of Competing Interest

The authors have nothing to disclose.

References

[1] Esposito E, Cassiano B, Cinquegrani F. Salivary glands: report of a rare case of myoepithelial carcinoma involving tongue base treated by CO2 laser. Acta Otorhinolaryngol Ital 2009;29:156–9.

[2] Miliauskas JR, Orell SR. Fine-needle aspiration cytological findings in five cases of epithelial-myoepithelial carcinoma of salivary glands. Diagn Cytopathol 2003;28:163–7.

[3] Shinozaki A, Nagao T, Endo H, et al. Sebaceous epithelialmyoepithelial carcinoma of the salivary gland: clinicopathologic and immunohistochemical analysis of 6 cases of a new histologic variant. Am J Surg Pathol 2008;32:913–23.

[4] van Tongeren J, Creytens DH, Meulemans EV, de Bondt RB, de Jong J, Manni JJ. Synchronous bilateral epithelial-myoepithelial carcinoma of the parotid gland: case report and review of the literature. Eur Arch Otorhinolaryngol 2009;266:1495–500.

[5] Vázquez A, Patel TD, D'Aguillo CM, Abdou RY, Farver W, Baredes S, et al. Epithelial-myoepithelial carcinoma of the salivary glands: an analysis of 246 cases. Otolaryngol Head Neck Surg 2015;153:569–74.

[6] Angiero F, Sozzi D, Seramondi R, Valente MG. Epithelialmyoepithelial carcinoma of the minor salivary glands: immunohistochemical and morphological features. Anticancer Res 2009;29:4703–9.

[7] Teppo H, Paronen I. Epithelial-myoepithelial carcinoma in minor salivary gland of the hard palate. J Craniofac Surg 2008;19:1689–91.

[8] Gore RM et al. Epithelial-myoepithelial carcinoma: a population-based survival analysis BMC Ear. Nose Throat Disorders 2018;18:15.

[9] Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. Am J Surg Pathol 2007;31:44–57.

[10] Kane et al. Myoepithelial carcinoma of the salivary glands: a clinicopathologic study of 51 cases in a tertiary cancer center. Arch Otolaryngol Head Neck Surg 2010;136.

[11] Jiang et al. The prognostic significance of p63 and Ki-67 expression in myoepithelial carcinoma. Head Neck Oncol 2012;4:9.

[12] Deere H, Hore I, McDermott N, Levine T. Epithelial-myoepithelial carcinoma of the parotid gland: a case report and review of the cytological and histological features. J Laryngol Otol 2001;115:434–6.

[13] Simpson RHW, Clarke TJ, Sarsfield PTL, Gluckman PGC. Epithelial–myoepithelial carcinoma of salivary glands. J Clin Pathol 1991;44:419–23.