Radiotherapy and Oncology 134 (2019) 211–219

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

# Adjuvant radiotherapy for Merkel cell carcinoma: A systematic review and meta-analysis

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ARTICLE INFO

*Article history:*
Received 13 November 2018
Received in revised form 17 February 2019
Accepted 18 February 2019
Available online 28 February 2019

*Keywords:*
Merkel cell carcinoma
Adjuvant radiotherapy
Meta-analysis

ABSTRACT

Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy with a high propensity for local recurrence and regional and distant metastases. The main treatment is surgery with narrow excision margins and draining nodes, plus or minus adjuvant radiotherapy (RT) on the surgical bed and/or lymph nodes. We performed a systematic review and meta-analysis of the benefits of adjuvant RT in MCC treatment. PubMed, EMBASE, and the Cochrane Library were systematically searched to identify relevant studies published before September 2018. Prospective trials and retrospective series comparing adjuvant RT vs. no RT in resected primary MCCs were included. Primary endpoint was to evaluate the outcomes of MCC patients who received adjuvant RT in term of overall survival (OS) and disease-free survival (DFS). Hazard ratios (HRs) for OS and DFS were aggregated according to a fixed or random effect model. Secondary endpoints were local, locoregional, and distant DFS.

A total of 17,179 MCCs across 29 studies were analysed. There was a significant difference in OS between the RT and no RT arms (HR = 0.81, 95%CI 0.75–0.86, $P < 0.001$). There was also a significant difference in DFS in favour of adjuvant RT (HR = 0.45, 95%CI 0.32–0.62, $P < 0.001$). Adjuvant RT improved locoregional DFS and local DFS but not distant DFS (HR = 0.3, 95%CI 0.22–0.42; HR = 0.21, 95%CI 0.14–0.33, and HR = 0.79, 95%CI 0.49–1.14, respectively). Meta-regression analysis showed that high Newcastle–Ottawa scale scores, stage I–II MCCs, shorter follow-up durations, size >2 cm, and being of a younger age were associated with increased OS. This systematic review and meta-analysis suggests a survival and DFS benefit for postoperative radiation of MCCs. Intermediate stage MCCs derive the maximum benefit with local and regional relapses reduced by 80% and 70%, respectively. Conversely, distant metastases were not significantly prevented.

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Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous malignancy with a high propensity for local recurrence and regional and distant metastases. Primarily affecting the elderly (average age of presentation is 69 years), the incidence of MCC is slightly higher in men and occurs most commonly in sun-exposed areas of the body (50% head and neck, 40% extremities) [1]. MCCs are considered rare tumours that have almost tripled in incidence over the last 25 years; from a rate of 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001. This increase is probably due to ameliorated diagnostic tools and developed knowledge on the link between immunosuppression and MCC [2].

Considering the biological aggressiveness of MCCs, there is an unmet need regarding the optimal diagnostic and therapeutic approach. This need has become more and more obvious over the past years due to the realisation that MCCs have an extremely high rate of regional lymphatic involvement, i.e., from 15% to 35% of cases. Even in low-risk cases, occult nodal positivity has been shown to occur in 15–20% of cases [3]. Unfortunately, the rarity of this tumour has made it difficult to conduct prospective trials.

There is particular concern regarding adjuvant treatments (e.g., radiotherapy [RT], and chemotherapy) due to the lack of prospective trials. MCCs are highly radiosensitive tumours and published studies have suggested that there is an association between the use of adjuvant RT and a reduced risk of loco-regional recurrence. Among the positive studies, a limited effect of adjuvant RT on the

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https://doi.org/10.1016/j.radonc.2019.02.015
0167-8140/

disease's local recurrence has been reported for specific patient subpopulations with a high risk of recurrence. At present, no trials have shown a significant effect of adjuvant RT on overall survival (OS), while a small number of trials have observed a significant increase in disease-free survival (DFS). In a previous systematic review, the survival benefit of RT was observed at both the one- and three-year timepoints [4].

High-risk subpopulations have been differently defined in studies according to site of primary tumour (most retrospective analyses were conducted on head and neck primary MCCs), stage of disease (I versus IIa and IIb), type of excision margins (close versus extended), and type of lymph node resection (sentinel node biopsy versus complete loco-regional nodal dissection) and node involvement [5]. The same studies have observed a 'low-risk patient subpopulation' in which adjuvant RT seemed to have a lower/non-significant effect on reducing the risk of local recurrence (for example those with stage I MCC and with negative sentinel node biopsy). This subpopulation could potentially avoid adjuvant RT [6].

Most investigations were limited by small sample sizes, a lack of patient follow-up data, and a lack of matched comparison groups [5]. RT at both the primary MCC site and the regional lymph node bed is becoming widely adopted, however, even without compelling supportive data and without a consensus on RT schedule and volume [7]. This article aims to analyse the literature on the current MCC primary site therapeutic approach and explore the controversial role of adjuvant RT in MCC treatment.

## Material and methods

### *Selection of studies and inclusion criteria*

We searched PubMed, EMBASE, and the Cochrane Library for relevant studies published before 31 August 2018. The entry terms for the search were *("Merkel cell carcinoma"[All Fields] OR "Merkel carcinoma"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms])*. The following inclusion criteria were adopted: randomised/prospective trials or retrospective studies reporting data with the addition of adjuvant RT in at least 20 non-metastatic MCC patients. Principal exclusion criteria were overlapping publications, lack of relevant outcome data, and no surgical treatment in the control arm. If more than one publication was found for the same trial, the most recent, complete, and updated version was included in the final analysis. The quality of the randomised studies was assessed using the Jadad 5-item scale, which considers randomisation, double blinding, and withdrawals. The final score ranged from 0 to 5 [8]. The assessment of the risk of bias in retrospective studies was conducted independently by two authors using the Newcastle–Ottawa scale (NOS) [9].

### *Data extraction and endpoints*

The data extraction was conducted independently by three co-authors (FP, AG, and AC) according to the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. Any discrepancies were resolved by consensus between these three authors. The data extracted for each trial were: first author's name, year of publication; study type; number of evaluable patients; median age and follow up; stage, site, and size of primary tumour; type of surgery; margin status; dose and type of RT; toxicity; and the hazard ratios (HRs) for DFS and OS with the relative 95% confidence intervals (CIs). OS and DFS were the primary endpoints evaluated in the experimental (surgery + RT) and control arms based on the HRs and relative 95% CIs. Local, locoregional, and distant DFS (L-DFS, LR-DFS, and D-DFS) were the secondary endpoints.

### *Statistical analysis*

The HRs for DFS, OS, L-DFS, LR-DFS, and D-DFS with the relative 95% CIs were extracted from each study. Summary HRs were calculated using random- or fixed-effects models depending on the heterogeneity of the included studies. We also calculated the relative risk (RR) for all recurrences (excluding deaths) and the CIs of events in patients assigned to the RT arm compared to the control arm (surgery alone) for each study. Statistical heterogeneity between the trials included in the meta-analysis was assessed using the Chi [2] test and inconsistency was quantified with the $I^2$ statistic [10].

The assumption of homogeneity was considered invalid for $P$ values lower than 0.1. When substantial heterogeneity was not observed, the pooled estimate based on the fixed-effects model was reported using the inverse variance method. When substantial heterogeneity was observed, the pooled estimate based on the random-effects model was reported using the DerSimonian et al. method [11], which considers both within- and between-study variations. A two-tailed $P$ value lower than 0.05 was considered significant.

Potential publication bias was determined by visually evaluating the asymmetry of the funnel plot. Begg's and Egger's tests were also used to quantitatively detect publication bias [12,13]. The trimmed values using Duval and Tweedie's method are presented in the results section only if the two-tailed $P$ value was lower than 0.1 in the Egger's test. A leave-one-out sensitivity analysis was performed by iteratively removing 1 study at a time to confirm that our findings were not driven by any single study.

The statistical analyses were performed using the RevMan software for meta-analysis (v.5.3).

## Results

Initially, 1023 potentially relevant articles were retrieved, leaving a total of 701 articles after the elimination of duplicates. A total of 665 articles comprising irrelevant papers, reviews, case reports, meta-analyses, and studies with less than 20 patients were excluded based on the titles and abstracts (Fig. 1). The remaining 36 articles were then further reviewed based on the inclusion criteria described above to assess their suitability. Seven overlapping series or studies that did not provide HRs or survival curves were excluded.

Finally, 29 studies were included in the final meta-analysis [1,2,5–7,14–34,3,35–37]. Among these, only one was a randomised trial. The 29 eligible studies involved a combined total of 17,179 patients, among which 7819 underwent RT on the primary tumour and/or lymph-nodes. The enroled number of patients per study ranged from 24 to 6908. All included studies that were conducted abroad were published between 1990 and 2018. Most studies included stage I–II MCCs (78%), while 18% included stage III, 3% unknown, and 1% stage IV. Fifty-five percent of MCCs were located in the head and neck regions. The characteristics of the included studies and main outcomes are provided in Tables 1 and 2. Data regarding toxicities were only provided in two studies, therefore, they were not analysed.

### *Effect of adjuvant RT on OS*

Data on OS were available in 20 studies and data on disease-specific survival were available in one publication. There was a significant difference in OS between the RT and no RT arms (HR = 0.81, 95%CI 0.75–0.86, $P < 0.001$; $I^2 = 0\%$, $P = 0.47$; fixed effect model; Fig. 2). The results were similar when a random effect model was used (HR = 0.81, 95%CI 0.76–0.87; $P < 0.001$). After exclusion of the 5 largest, registry-based studies, the final result

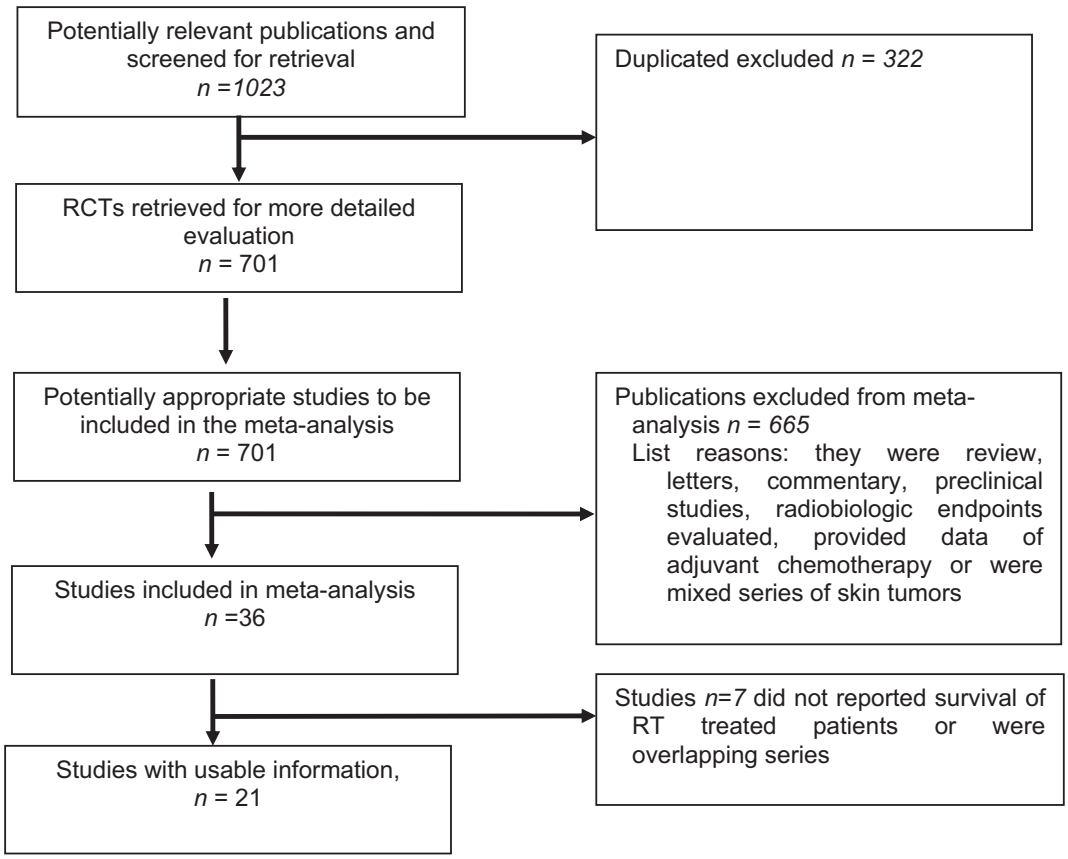


**Fig. 1.** Flow diagram of included studies.

was similar to the main analysis (HR = 0.78, 95%CI 0.64–0.92; $P = 0.004$; $I^2 = 0\%$).

*Effect of adjuvant RT on DFS*

Data on DFS were available in 15 studies and, among them, data on relapse-free survival were provided in three of these studies. There was a significant difference in DFS in favour of adjuvant RT (HR = 0.45, 95%CI 0.32–0.62, $P < 0.001$; $I^2 = 69\%$, $P < 0.001$; Fig. 3).

*Effect of adjuvant RT on locoregional, local, and distant DFS*

Data for regional, local, and distant control were available in five, seven, and two studies, respectively. Adjuvant RT improved LR-DFS and L-DFS but not D-DFS (HR = 0.3, 95%CI 0.22–0.42; HR = 0.21, 95%CI 0.14–0.33, and HR = 0.79, 95%CI 0.49–1.14, respectively) despite risk of distant metastases analysis derives from two publications and this flaws the power of the result.

*Sensitivity analysis*

To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the summary HR. The summary HRs remained stable (range 0.79–0.81), indicating that our results were not driven by any single study reporting OS data.

*Publication bias*

The analysis of OS was found to have a publication bias according to the Egger test ($p = 0.07$) and to the visual inspection of the funnel plot (Fig. 4). These values remained unchanged after using the trim and fill method. To further explore the potential sources of the heterogeneity observed in this analysis, we excluded each study sequentially to determine its effect on the main summary estimate. HRs ranged from 0.792 (excluding the trial of Mojica et al.[27]) to 0.814 (excluding the trial by Jabbour et al.[23]). The meta-regression analysis showed that high NOS scores, stage I–II MCCs, shorter follow-up durations, size >2 cm, and being of a younger age were associated with increased OS.

## Discussion

Our meta-analysis of studies where adjuvant RT was delivered after surgery for MCC suggests a possible survival benefit and a major contribution to locoregional control, with the exception of distant metastases for postoperative radiation. From regression analysis, it seems that optimal primary treatment with radical surgery and adjuvant RT to the bed and/or draining lymph nodes is appropriate for stage I–II MCCs that are at least 2 cm in size. The adjuvant treatment for MCC remains controversial because there is a lack of data on which to base treatment algorithms, recommendations, and guidelines. A lower number of retrospective studies have collected data on the optimal treatment of MCC that is either in the advanced or initial stages.

Although patients are generally treated with surgery as first-line approach, there is still some controversy regarding the extent of surgical intervention. It is important to note that these observations came from melanoma and other cutaneous tumour surgical recommendations (i.e. Mohs surgery and sentinel node biopsy). More doubtful is the role of adjuvant RT in improving the clinical outcomes of MCC patients because the evidence is derived from retrospective series or small prospective cohorts. Furthermore,

**Table 1**
Characteristics of included studies.

| Author/year | Type of study | N° of pts | Median follow up (months) | Median age | Site of primary tumour (%) | | | Size (cm) % | Stage (%) | Type of surgery (%) | R+ % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | H&N | Trunk | Extremities | | | | |
| Asgari/2014 | Retrospective | 218 | 75.6 | 77 | 45 | 3.7 | 51.3 | <2 (35%)<br>>2 (11)<br>Unknown (53.7) | I–II (57.8)<br>III (25.7)<br>IV (16.1) | – Surgery ± SLNB ± LN dissection | 6.9 |
| Balakrishnan/2013 | Retrospective | 54 | 22 | 76 | 100 | 0 | 0 | NR | I–II (96)<br>III (4) | – WLE (72)<br>– Other (11) | 21 |
| Bhatia/2016 | Retrospective | 6908 | NR | 76 | 44 | 12 | 44 | <2 (39)<br>>2 (61) | I–II (70)<br>III (30) | – WLE ± SNB (stage I-II) or LN dissection (only in stage III) | 12 |
| Boyer/2002 | Retrospective | 45 | 27.5 | 72 | 69 | 2 | 28.5 | 1.3 (median) | I (100) | – Mohs surgery or WLE | NR |
| Chen/2015 | Retrospective | 4815 | NR | NR | 100 | 0 | 0 | <2 (65)<br>>2 (35) | I–II (27)<br>III (73) | – WLE (92) or Mohs surgery (8) | 21 |
| Clark/2007 | Retrospective | 110 | 21.6 | 70 | 100 | 0 | 0 | NR | I–II (52)<br>III (17)<br>Unknown (56) | – WLE (93) + LN dissection (45) | 35 |
| Eich/2002 | Retrospective | 31 | 22 | 70 | 42 | 16 | 42 | NR | I–II (97)<br>III (3) | – WLE (100)<br>– WLE + LN dissection (55) | 0 |
| Fields/2011 | Retrospective | 364 | 43.2 | 70 | 36 | 17 | 38 | <2 (75)<br>>2 (25) | I–II (74)<br>III (26) | – WLE (29)<br>– WLE + SNB (33)<br>– WLE + LN dissection (38) | 7 |
| Ghadjar/2011 | Retrospective | 180 | 60 | 73 | 50 | 18 | 22 | NR | I–II (100) | – WLE (93) or biopsy (7) | 35 |
| Gillenwater/2001 | Retrospective | 66 | NR | 68.4 | 100 | 0 | 0 | <2 (67)<br>2–5 (15%)<br>>5 (6)<br>NR (9) | cN+ (11)<br>cN0 (77)<br>cNX (9) | – WLE ± neck dissection + RT (51)<br>– WLE ± neck dissection (39)<br>– RT (9) | NR |
| Howle/2012 | Retrospective | 136 | 38 | 75 | 47 | 7 | 29 | 1.1 (median) | I (66)<br>II (34) | – Surgery alone (39)<br>– Surgery + CT (1)<br>– Surgery + RT (51)<br>– Surgery + CTRT (4)<br>– RT alone (6) | 66 |
| Jabbour/2007 | Retrospective | 82 | 23 | 72 | 54 | 1 | 35 | <2 (79)<br>2–5 (13)<br>>5 (5) | I (61)<br>II (35) | – WLE (89) + LN dissection (35)<br>– Adj RT (82)<br>– Adj CTRT (11) | 30 |
| Jouary/2011 | Randomized | 83 | 57.7 | 70.9 | 43.4 | 6 | 50.6 | NR | I (100) | – WLE + RT on tumour bed (100) | 0 |
| Kang/2012 | Retrospective | 62 | 44 | 74 | 51 | 5 | 27 | 15 (5–60) | I–II (68)<br>III (32) | – WLE or excisional biopsy (80) | 0 |
| Kim/2013 | Retrospective | 747 | NR | 76 | 40 | 13 | 47 | <2 (61)<br>>2 (39) | I–II (53)<br>III (47) | – Local tumour destruction or WLE (100) + SLNB or nodal dissection (22.8) | NR |
| Meuwissen/1995 | Retrospective | 80 | 20 | 74 | 100 | 0 | 0 | <2 (66)<br>2–5 (16)<br>NR (16) | I–II (67)<br>III (33) | – Radical surgery (90) + LN dissection (11)<br>– Incomplete surgery (9) + LN dissection (15)<br>– CTRT (1) | NR |
| Mojika/2007 | Retrospective | 1187 | 40 | 74 | NR | NR | NR | 2 (median) | I–II (55)<br>III (31)<br>IV (6) | – WLE (82)<br>– Radical surgery + LN dissection (10) | NR |
| Morrison/1990 | Retrospective | 54 | NR | 70 | 70 | 14 | 16 | <2 (78)<br>>2 (22) | I–II (83)<br>III (17) | – WLE (91) + LN dissection (5)<br>– RT alone (9) | NR |
| Pectasides/2008 | Retrospective | 24 | 24 | 68 | 33 | 17 | 50 | NR | I–II (88)<br>III (12) | – WLE (67)<br>– WLE + LN dissection (21) | 0 |
| Poulsen/2010 | Retrospective | 60 | 56 | 76 | 0 | 0 | 100 | NR | I (30)<br>II (20)<br>III (48) | – Surgery alone (28)<br>– Surgery + RT (48)<br>– Surg + CTRT (10)<br>– CTRT (5)<br>– RT alone (7)<br>– Other (2) | 10 |
| Rastrelli/2018 | Retrospective | 90 | 29 | 69 | 20 | 21 | 59 | <2 (21)<br>>2 (79) | I–II (42)<br>III (52)<br>IV (6) | – WLE ± SLNB ± LN dissection | NR |
| Reichgelt/2011 | Retrospective | 808 | NR | 76 | 44.2 | 9.7 | 39.6 | <2 (41)<br>>2 (21)<br>NA (14) | I (55)<br>II (31)<br>III (6) | – Surgical excision, with or without SNLB<br>– Surgical excision, with ELND<br>– Surgical excision, with RLND | NR |
| Senchenkov/2007 | Retrospective | 38 | NR | 66.6 | 0 | 0 | 100 | NR | I (71)<br>II (29) | – WLE (84)<br>– Mohs micrographic surgery (15) | NR |
| Servy/2016 | Retrospective | 87 | 39 | 70.7 | 31 | 11.5 | 57.5 | <2 (61)<br>≥2 (39) | I (100) | – WLE + SLNB (100) | NR |

**Table 1** (*continued*)

| Author/year | Type of study | N° of pts | Median follow up (months) | Median age | Site of primary tumour (%) | | | Size (cm) % | Stage (%) | Type of surgery (%) | R+ % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | H&N | Trunk | Extremities | | | | |
| Sexton/2014 | Retrospective | 42 | 54 | 70.5 | 42 | 26 | 32 | <1 (100) | I (100) | – WLE (100) + LN dissection or SLNB (20) | NR |
| Strom/2016 | Retrospective | 171 | 33 | 74 | 41.5 | 10.5 | 47.9 | 1.5 (median)<br>≤2 (42.1)<br>>2 (18.1)<br>NR (39.8) | pN0 (59.1)<br>pN1 (31)<br>cN1 (9.9) | – WLE (98.2), with (87.7) or without SNLB<br>– EB (1.8)<br>– LN dissection (12.3)<br>– CT (15.4)<br>– Adj RT (76) | 9.4 |
| Takagishi/2016 | Retrospective | 46 | 44.4 | 66.5 | 100 | 0 | 0 | <1 (85)<br>>1 (15) | I (100) | – WLE + SLNB (100) | 0 |
| Tarantola/2012 | Retrospective | 240 | NR | 70.1 | 46.3 | 6.7 | 38 | 1.37 (median) | I (31.3)<br>II (17.1)<br>III (23.3)<br>IV (2.1)<br>NR (26.3) | – EB (4.6)<br>– WLE (78.8)<br>– Mohs micrographic surgery (13.8)<br>– CT (12.5)<br>– Adj RT (42.1) | NR |
| Van Veenendaal/ 2018 | Retrospective | 351 | 28 | 74 | 49 | 11 | 31 | 17 (median) | I–II (42)<br>III (32)<br>IV (3)<br>Unknown (23) | – Surgical excision ± LN dissection | 14 |

WLE, wide local excision; EB, excisional biopsy; NR, not reported; RT, radiotherapy; CT, chemotherapy; SNLB, sentinel lymph node biopsy; ELND, elective lymph node dissection; RLND, radical lymph node dissection.

the majority of published studies are hampered by a marked heterogeneity of patient characteristics, e.g. mixed stages of disease; differences in surgical procedures performed prior to RT (biopsies, debulking, whole local excision, marginal status, lymph node sentinel evaluation); differences in or lack of information about performance status, comorbidity, immunosuppression condition, and tissue immunohistochemistry positivity for MCC polyomavirus; and adjuvant RT performed after surgery (radiation doses and volume, timing of RT, and whether RT was administered to only the primary tumour site, in the regional lymph nodes, or included in both sites).

Due to a lack of prospective comparative data, the international guidelines currently include adjuvant RT as a treatment 'option' for all stages of the disease (I––III) to be performed within four to six weeks of surgery, although it is still unclear which subgroups of patients with MCC can really reap the greatest benefits from treatment (NCCN 2019, EORTC 2015). In general, for large N0 MCCs, consensus panels and international guidelines (EADO/EORTC, NCCN) agree on the possible role of adjuvant RT after surgical excision for increasing local control in the primary tumour bed, whereas there is more uncertainty for patients in III (any tumour size with nodes positivity) except for cases with multiple affected lymph nodes of extracapsular extension [38,39]. Ideally, prospective studies are needed to identify which subgroups of patients in stage I–III could be recommended adjuvant RT treatment.

To date, the only prospective randomised trial for MCC was conducted by Jouary et al. in stage I patients treated with wide local excision and RT to tumour bed was randomized to adjuvant regional radiotherapy or to observation alone [24]. The trial was closed prematurely due to a drop in recruitment related to the introduction of the lymph node sentinel evaluation in the management of MCC. No significant improvement in OS or PFS was demonstrated after RT, however, a significant decrease in the risk of local recurrence when compared with the group under exclusive observation (0% vs. 16.7%, $P = 0.007$) was highlighted.

It is still not clear whether adjuvant RT improves DFS and OS in patients with node-negative disease rates or if it reduces the risk of local recurrence [15,7,6,33,40,41]. Even the results of retrospective studies regarding the clinical benefits of RT in patients with node-positive MCC (stage III) are often conflicting [15,19,6,40,42]. Evidence from the National Cancer Database [15] for 6908 patients has shown that adjuvant RT improves OS compared to surgery in stage I and II patients, but not in stage III patients. This was also confirmed in the multicentric retrospective study of Servy et al. [7], which evaluated the role of sentinel lymph node status and adjuvant RT. They concluded that survival in stage III MCC could be driven by the presence of subclinical distant metastases, which are often present in these patients, rather than adjuvant therapeutic approaches [19]. Conversely, the Moffitt Cancer Center's retrospective study of 171 patients showed that postoperative RT improves locoregional control and disease-specific survival in patients with positive lymph nodes, but not in patients with negative lymph nodes [6].

Our study has potential limitations, however. First, the use of a meta-analysis for observational studies is controversial and the heterogeneity of the studies' designs and patient populations may have affected the pooled estimation. All studies were not randomized in their nature, therefore, there could be a potential imbalance in patient characteristics (performance status and comorbidities), with more fit patients and with a more advanced disease that potentially could have received adjuvant RT. Although randomised controlled trials provide the most reliable evidence, such studies are currently lacking for MCC and a meta-analysis of retrospective or non-randomised studies might be appropriate to assess treatment efficacy for such rare disease. Despite the retrospective nature of most studies, the results were not driven by any single study reporting OS data and heterogeneity was absent. Second, the type of RT has changed over the years with modern application of RT delivery (e.g., IMRT) that now represents the standard of care. Furthermore, in the paper included, acute toxicities and long-term follow up of irradiated patients was not known. Finally, the contribution of adjuvant chemotherapy is not well known and is not evaluated in the present meta-analysis. It is likely that in stage III MCC, RT is not enough to delay the progression of the disease and increase survival without the addition of systemic therapy. Despite these limitations, our analysis suggests the possible use of postoperative radiation for MCC, at least for stages I–II, which are the most represented stages in this meta-analysis. Sur-

**Table 2**
Radiotherapy delivery and outcomes.

| Author/year | N° received RT/Type RT/target of RT (%) | Dose of RT (Gy) | OS<br>RT vs no RT | DFS<br>RT vs no RT | Locoregional-DFS<br>RT vs no RT | Local-DFS<br>RT vs no RT | Distant-DFS<br>RT vs no RT | Type of analysis | Quality of paper |
|---|---|---|---|---|---|---|---|---|---|
| Asgari/2014 | 71/NR/NR | NR | HR = 0.9 (0.6–1.3) | NR | 0.3 (0.1–0.6) | NR | 1.5 (0.8–3.1) | MVA | 7 |
| Balakrishnan/2013 | 46/NR/regional RT (NR) | 50 | HR = 0.37 (0.13–1.07) DSS | 0.63 (0.23–1.71) TTR | NR | NR | NR | UVA | 7 |
| Bhatia/2016 | 2976/NR/NR | NR | HR = 0.71 (0.64–0.80) for stage I<br>HR = 0.77 (0.66–0.89) for stage II<br>HR = 0.98 (0.86–1.12) for stage III | NR | NR | NR | NR | MVA | 6 |
| Boyer/2002 | 20/NR/T and N | 45–50 (T), 45–60 (N) | HR = 0.95 (0.26–3.51) DSS | NR | NR | NR | NR | UVA | 7 |
| Chen/2015 | 2330/NR/NR | NR | HR = 0.8 (0.7–0.92) | NR | NR | NR | NR | MVA | 6 |
| Clark/2007 | 66/NR/T (55) and N (60) | 50 | HR = 0.52 (0.25–1.07) | HR = 0.64 (0.37–1.12) | NR | NR | NR | MVA | 8 |
| Eich/2002 | 16/photons or electrons/T (56) or T + N (44) | 55 | NR | NR | NR | HR = 0.32 (0.11–0.93) SFLD | NR | UVA | 7 |
| Fields/2011 | 160/external beam/T (47) or N (53) | ≥50 | NR | NR | HR = 0.48 (0.24–0.97) | HR = 0.53 (0.13–2.19) | NR | UVA | 8 |
| Ghadjar/2011 | 131/NR/T (75) and N (21) | 50–60 | HR = 0.95 (0.57–1.58) | HR = 0.25 (0.16–0.41) | HR = 0.27 (0.16–0.49) | HR = 0.18 (0.07–0.43) | HR = 0.41 (0.23–0.75) | MVA | 8 |
| Gillenwater/2001 | 26/NR/T + N + surgical bed (100) | 46–66 | HR = 1.05 (0.54–2.05) | NR | NR | NR | NR | UVA | 6 |
| Howle/2012 | 69/NR/NR | 50 | HR = 0.94 (0.55–1.6) | HR = 0.27 (0.14–0.51) | NR | NR | NR | UVA | 8 |
| Jabbour/2007 | 48/Photons or electrons (89)/T (75) + N (64) | 50* | HR = 0.39 (0.18–0.82) | HR = 0.39 (0.2–0.75) | NR | NR | NR | MVA | 8 |
| Jouari/2011 | 39/photon (T) and photon + electron (N)/T (100) + N (50) | 50 | HR = 1.23 (0.39–4.54) | NR | NR | NR | NR | UVA | - |
| Kang/2012 | 43/electron (T) and megavoltage (N)/T (69) + N (69) | 46–50 | NR | HR = 0.33 (0.15–0.74) | HR = 0.16 (0.05–0.47)^ | HR = 0.05 (0.01–0.3)° | NR | UVA | 8 |
| Kim/2013 | 404/NR/NR | NR | HR = 0.78 (0.61–0.99) | NR | NR | NR | NR | UVA | 5 |
| Meuwissen/1995 | 51/electrons (T) and electrons or photons (N)/T + N (100) | 50 or 45–60 (R2 only) | NR | HR = 0.2 (0.11–0.37) | NR | NR | NR | UVA | 7 |
| Mojika/2007 | 477/NR/NR | NR | HR = 0.85** (0.75–0.96) | NR | NR | NR | NR | MVA | 6 |
| Morrison/1990 | 12/electrons/NR | NR | HR = 0.69 (0.3–1.57) | HR = 0.57 (0.27–1.22) RFS | NR | NR | NR | UVA | 5 |
| Pectasides/2008 | 11/NR/NR | NR | HR = 0.53 (0.13–2.14) | HR = 0.46 (0.16–1.33) | NR | NR | NR | UVA | 6 |
| Poulsen/2010 | 42/NR/T (50) + N (59) | 48–49 | NR | HR = 0.51 (0.05–4.76) RFS | NR | NR | NR | MVA | 8 |
| Rastrelli/2018 | 32/NR/NR | NR | HR = 0.87 (0.45–1.7) | HR = 2.72 (1.28–5.77) RFS | NR | NR | NR | UVA | 7 |
| Reichgelt/2011 | 259/NR/NR | NR | HR = 0.82 (0.65–1.04) | NR | NR | NR | NR | MVA | 6 |
| Senchenkov/2007 | 21/NR/tumour bed and regional N | 46–61 | HR = 0.52 (0.16–1.66) | NR | NR | HR = 0.29 (0.1–0.85) | NR | MVA | 8 |
| Servy/2016 | 75/NR/tumour bed and regional N | 50 | HR = 0.16 (0.05–0.51) | HR = 0.19 (0.07–0.50) | NR | NR | NR | MVA | 8 |
| Sexton/2014 | 18/NR/T (24) + N (20) | NR | NR | HR = 0.68 (0.29–1.58) | NR | NR | NR | UVA | 8 |
| Strom/2016 | 130/NR/T + N | 50 (40–66) | HR = 0.53 (0.21–0.93) | HR = 0.42 (026–0.7) | HR = 0.28 (0.14–0.56) | HR = 0.18 (0.07–0.46) | NR | MVA | 8 |
| Takagishi/2016 | 23/photons and/or electrons/T (100) + N (26) | 50 (16–66) | HR = 0.9 (0.23–3.5) | NR | NR | HR = 0.15 (0.03–0.76) | NR | UVA | 8 |
| Tarantola/2012 | 101/NR/NR | NR | HR = 0.82 (0.44–1.53) | NR | NR | NR | NR | UVA | 8 |
| Van Veenendaal/2018 | 122/NR/T (65) and N (35) | 60 | HR = 1.1 (0.6–1.8) | HR = 0.54 (0.3–0.9) | NR | NR | NR | MVA | 8 |

TTR, time to recurrence; Mo, months; SFLD, survival-free of local disease; RFS, relapse-free survival; NR, data not available.
* Median dose.
° Stage I–II that received local RT.
^ Patients having regional RT.
** Out of 603 patients with data available.

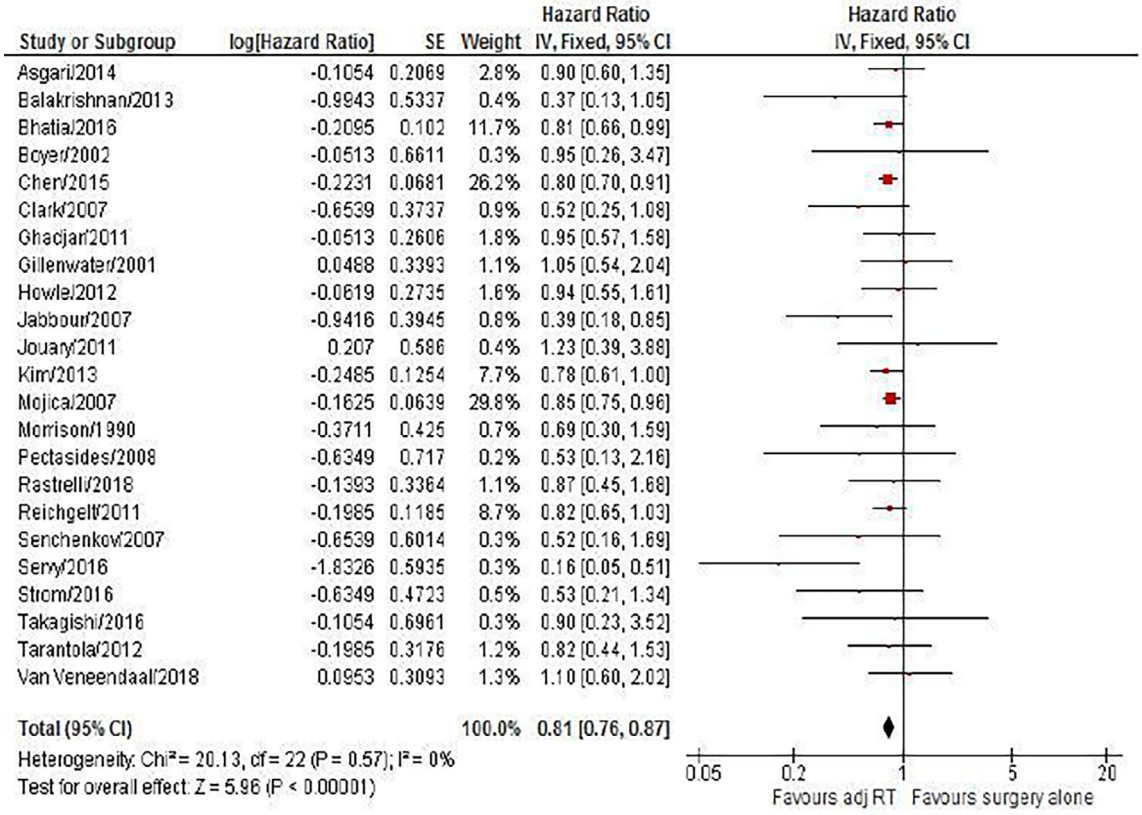


**Fig. 2.** Forrest plot for overall survival analysis.

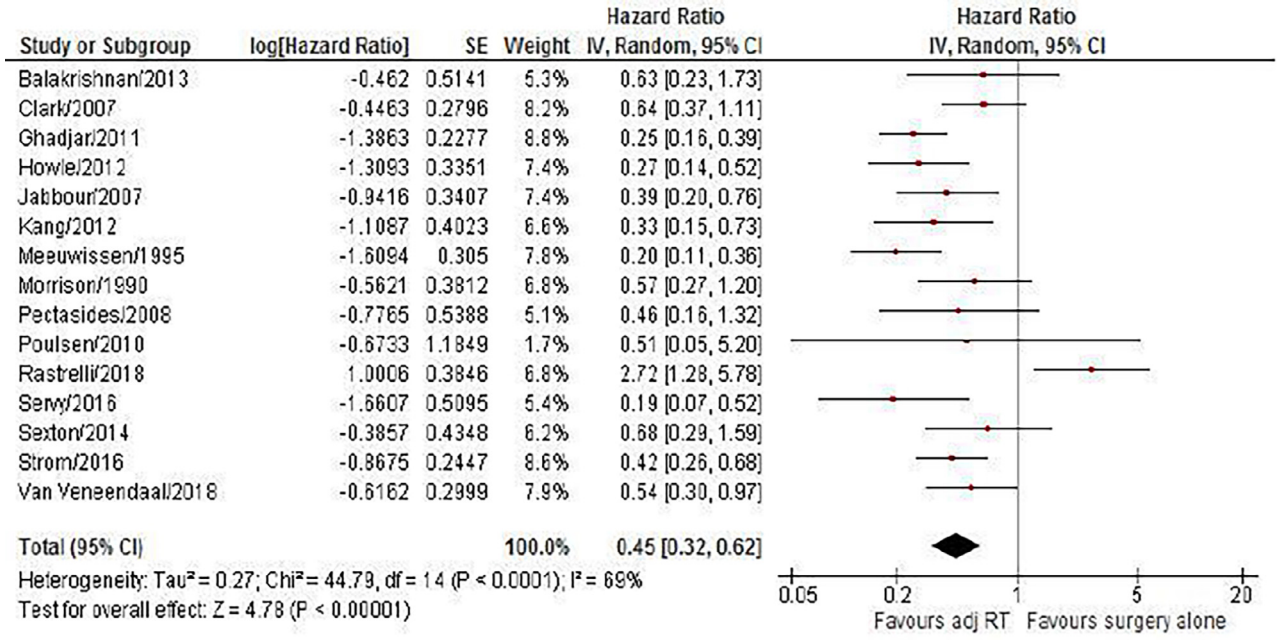


**Fig. 3.** Forrest plot for disease-free survival analysis.

vival data are robust and the results did not change even after exclusion of largest registry-based series.

In summary, it should be specified that due to the rarity of the disease, the therapeutic approach for MCC must always be decided by a multidisciplinary group comprising a dermatologist, oncologist, radiotherapist, and surgeon in reference centres dedicated to the treatment of neuroendocrine tumours. In reality, however, the choice of treatment is more often defined by a single specialist. This issue further worsens the heterogeneity of the data that are often evaluated in retrospective studies.

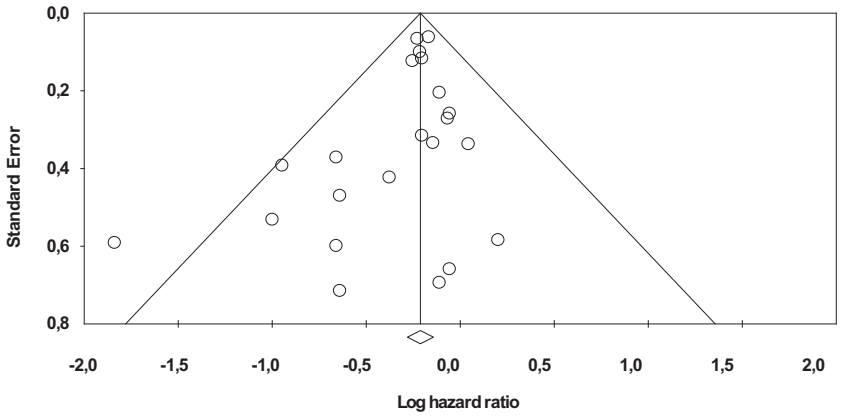


**Fig. 4.** Funnel plot for publication bias in overall survival analysis.

We are cautious about recommended adjuvant RT for all patients with MCC and we believe that this treatment should be discussed by a multidisciplinary expert team and aimed at patients with a significantly high risk of local or lymph node recurrence. Therefore, we suggest several prognostic factors should be considered, such as the size of the primary tumour (>2 cm, stage II); the pathological positivity of lymph nodes or sentinel lymph nodes (stage III) or the absence of a correct assessment of the pathological lymph node status; an immunosuppression condition, such as HIV, lymphoproliferative diseases, and organ transplantation; and the presence of lymphatic and vascular invasion on pathological examination and/or positive state of margins after surgical resection.

We believe that RT may not benefit pathologically node-negative patients with very small primary tumours (<2 cm, stage I). Indeed, the absence of a clear and well-defined standard adjuvant algorithm compared to a personalised approach highlights the need to perform prospective studies and randomised trials with a homogeneous cohort of patients regarding stages (lymph nodes or SLNB positive versus negative), histopathologic characteristics (tumour size, marginal status, vascular and lymphatic invasion, IHC stain for Merkel cell polyomavirus), and treatments (extension of the resection and fields of radiation treatment to unify the therapeutic approach). Unfortunately, there are no prospective clinical trials currently evaluating the role of adjuvant RT in MCC treatment.

Despite data about adjuvant RT for MCC derive from retrospective or observational studies, this meta-analysis suggests that it may be offered to patients' resected MCC.

## Conflict of interest

None.

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