

Outcome of early stage Merkel carcinoma treated by exclusive radiation: a study of 53 patients.

Manon DUBOIS (✉ manon.dubois.3@gmail.com)

CHU Lille <https://orcid.org/0000-0002-8465-4225>

Henry Abi Rached

Hopital Claude Huriez

Alexandre Escande

Centre Oscar Lambret

Frédéric Dezoteux

Hôpital Claude Huriez: Hopital Claude Huriez

Franck Darloy

Centre Léonard de Vinci

Anaïs Jouin

Les Dentellières

Maeva Kyheng

CHU Lille

Julien Labreuche

CHU Lille

Veronique Dziwniel

Centrale Lille

Xavier Mirabel

Centre Oscar Lambret

Laurent Mortier

Hopital Claude Huriez

Research

Keywords: Exclusive radiation, Merkel cell carcinoma, Skin cancer

Posted Date: February 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-100185/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Radiation Oncology on May 14th, 2021. See the published version at <https://doi.org/10.1186/s13014-021-01815-4>.

Abstract

Purpose: Early stage Merkel cell carcinoma (MCC) is a rare and aggressive primary skin cancer. The standard of care for MCC is broad excision and adjuvant external beam radiation therapy (EBRT). However, for some patients, anesthesia is contraindicated, while others run the risk of serious aesthetic sequelae. In such cases, exclusive radiotherapy is an interesting alternative to surgery. Though limited data is available, this study evaluates exclusive radiotherapy for MCC, using data from the largest retrospective study to date.

Methods: All patients who were followed in our center between 1989 and 2019 for histologically proven early stage MCC were included in the study. They were treated either by surgery with a 2-cm clear margin followed by adjuvant radiotherapy (RT) or by exclusive RT. Survival rates with adjuvant and exclusive EBRT were analyzed using Cox model and Fine & Gray model depending on the type of survival. P-value < 0.05 was considered significant

Results: Eighty-four patients treated for MCC were included. Fifty-three of them (63.1%) were treated by exclusive RT, and 31 (36.9%) had surgical excision followed by adjuvant RT. Local relapse rate was 13.7% (95%CI 8.0-43.7) in the RT monotherapy group (group A) and 25.8% (95%CI 10.3-56.2) in the surgery + RT group (group B) ($p = 0.42$). No statistical difference was found for nodal relapse ($p = 0.81$), metastatic relapse ($p = 0.10$), disease free survival ($p = 0.83$) or overall survival ($p = 0.98$).

Conclusion: Our study suggests that exclusive radiotherapy for early Merkel cell carcinoma leads to a similar oncological outcome as combined treatment, with fewer aesthetic sequelae. The approach is interesting for elderly patients with comorbidities or patients for whom surgery would cause significant functional or aesthetic sequelae.

1. Introduction

Merkel cell carcinoma (MCC) is a rare but aggressive skin cancer. Its overall incidence has increased over the past 20 years and varies between 0.1 and 1.6/100,000 [1]. It frequently affects the elderly, with a mean age of 74.9 years [1] and immunosuppressed patients [2–4]. The primary tumor is frequently located on sun-damaged skin, especially in the head and neck region.

It is an aggressive tumor, with 5-year survival rate of 64% for patients with localized tumors, 39% for patients with tumors with lymph nodes involvement and 18% at the metastatic stage [5]. In addition, patients face an estimated 35% risk of local recurrence, a 40% risk of lymph node recurrence and a 20% risk of metastatic recurrence after surgery [6].

At localized stage, wide surgical excision with a 2 to 3 cm margin followed by radiotherapy (RT) (doses ranging from 50 to 66 Gy) is the recommended treatment [7,8]. Post-surgical functional sequelae could majorly alter the quality of life in the elderly population, making exclusive RT an interesting option in this population. Some authors suggest that margins of 1 to 2 cm may be sufficient, when using Mohs'

micrographic surgery which includes histologic examination of tissue edges and aim to spare as much healthy tissue as possible [8]. In patients with negative clinical lymph nodes, it is recommended to perform a sentinel lymph node biopsy (SLNB) and, if the SLNB is positive, a lymph node resection and RT. At the metastatic stage, chemotherapy or immunotherapy is proposed.

In daily clinical practice, surgical techniques may be limited either by aesthetic and major functional sequelae or by anesthesia contraindication. Exclusive radiotherapy may be an effective alternative, as MCC is known to be a radiosensitive tumor [9]. Indeed, several authors have observed that a treatment of MCC patients by exclusive radiotherapy leads to good outcomes [10–13].

The aim of this study was to compare exclusive radiotherapy to the gold standard treatment (surgery followed by radiotherapy) in localized MCC.

2. Methods

Population and treatment:

We reviewed the medical records of patients referred to our department of dermatology and treated with curative intent for MCC. Patients' data were collected in computerized and anonymized medical files using a unique identifier for each patient, then stored in a secured file for statistical analysis. This included patients with localized MCC, who presented a solitary tumor. Lymph node involvement was assessed by imaging (either by ultrasound or CT scan) and/or by SLNB. Patients with a positive SLNB or lymph node metastasis were excluded. Patients were divided into two groups: group A for patients with a unique, non-resected MCC at the time of RT and group B for patients who had surgery with a 2 cm margin followed by adjuvant RT. Patients treated by surgery with a margin smaller than 2 cm or by surgery without adjuvant RT were excluded. The RT technique varied based on according to the treatment center, the time of treatment and the patient (2D, 3D, intensity-modulated radiotherapy, cobalt or photon radiotherapy).

Our primary objective was to compare the local relapse rate in the two groups. We defined the local relapse as a confirmed MCC relapse in the irradiated area.. Our secondary objectives were to compare the nodal relapse, metastatic relapse, disease-free survival (DFS) and overall survival (OS) rates in the two groups.

Statistical analysis:

Data are expressed as numbers (percentages) for categorical variables, and median and interquartile ranges (IQR) for quantitative variables. We estimated the cumulative incidence of specific recurrence events (local, nodal and metastatic) and specific mortality by using the approach of Kalbfleisch and Prentice[14], treating non-specific death (according study outcome) as competing risk.

We investigated the associations between the type of surgery (i.e., RT monotherapy group and surgery + RT group) and the occurrence of specific recurrences in univariable and multivariable Fine-Gray models

adjusted on pre-specified parameters: age, size, radiation dose on the lesion, radiation dose on the draining lymph nodes and localization. All these factors are known as prognostic factors for MCC in the literature.

The rates of overall survival (OS) and disease-free survival (DFS defined as the time to any recurrence of death) were estimated using the Kaplan-Meier method. The impact of the type of surgery was analyzed using the univariable and multivariable Cox model regression with similar prespecified adjustments. The proportional hazard assumption was checked by examining the Schoenfeld residuals[15]. The same pre-specified adjustments as above were applied.

Confidence intervals of 95% using loglog methods (CI95%) were used. All statistical tests were done at the two-tailed α level of 0.05. Data were analyzed using SAS version 9.4 [SAS Institute Inc., Cary, NC 27513, USA].

Ethics:

According to the standard procedure and the Jardé Law (March 2012) on the publication of retrospective data, all the patients of the study expressed their non-opposition to the use of their anonymized medical data. The study has been declared to and accepted by the CNIL (Commission Nationale Informatique et Libertés, the organization in charge of the ethical use of data collected for scientific purposes in France (DEC19-373)).

3. Results

Patients characteristics:

Between 1989 and 2019, 175 patients with stage I-II MCC were treated, then underwent clinical and imaging follow-up (lymph node imaging and/or body CTscann) once every 3 months for 3 years then once every 6 months for 2 years. Patients who did not relapse were subsequently followed up with a clinical examination once a year by their dermatologist. Eighty-four patients (48.0% of the 175 patients) were included in the study: Fifty-three (63.1%) in group A and 31 (36.9%) in group B. Of the 91 patients (52.0%) excluded, 84 (92.3% of the 91 patients excluded) were excluded because they had undergone surgery with margins smaller than 2 cm, two (2.1%) were excluded because of palliative or hemostatic RT, and five (5.5%) were excluded because they had undergone surgery without RT. The study flow diagram is shown in Figure 1.

The median tumor diameter was 2.0 cm ((IQR 1.2-4.0); ranging from 0.4 to 9 cm) in group A and 2.5 cm ((IQR 1.8-4.0); ranging from 1.2 to 8 cm) in group B. The primary tumor was located in the head and neck region for 43 patients in group A (81.1%) and only eight patients in group B (23.3%). Eight patients (15.0%) in group A had hematological diseases (5 chronic lymphocytic leukemias and three lymphomas), compared to three patients (9.7%) in group B (One chronic lymphocytic leukemia and one lymphoma). The patients in group A were ineligible for surgery either because of the location and/or size of the tumor

(32 out of 41 patients, or 78.0%, missing data for 12 patients) making surgery too decaying or because comorbidities or bad general conditions contraindicating anesthesia (8/41 patients, or 19.5%). One patient refused surgery. The patients' baseline characteristics are presented in *Table 1*.

Treatment characteristics:

Most patients received conventional external beam radiotherapy (EBRT) (daily treatment of 2 Gy, 5 fractions a week). Three patients out of 53 in group A (5.6%) were treated with hypofractionated RT (decrease in the number of fractions, but dose per session > 2.2Gy, median doses of 45 Gy (EQD2 = 48.75 Gy). Median EBRT doses of 60.0 Gy (IQR 50-65) were delivered on the primary tumor with large irradiation fields. Seven patients in group A (13.2%) received 45 Gy or less because of bad tolerance or treatment impact on general well-being. In group B, patients had surgery with margins > 2 cm (maximum 3 cm), followed by adjuvant RT with a median dose of 50 Gy (IQR 50 to 54Gy). Four patients in group B (but none in group A) had a negative SLNB.

We performed prophylactic irradiation of the draining lymph nodes and of the area between the primary tumor site and the draining lymph nodes in 64 patients (76.2%). This included 40 out of the 53 patients in group A (75.5%) and 24 out of the 31 patients in group B (77.4%). The median dose was 50 Gy (IQR 50 to 53) in group A and 50 Gy (IQR 50 to 55) in group B. The treatment characteristics are presented in *Table 1*.

Outcomes:

The median follow-up was 64 months (CI95% 38 – 148 months) for group A and 95 months (CI95% 42 – 244 months) for group B ($p = 0.26$). At the end of the follow-up, 57 out of the 82 patients (69.5%) presented a relapse or died (while 27 patients presented local or distant relapse). Of the 57 patients who presented a relapse or died, 34 were in group A (66.6%) and 23 in group B (74.2%) in group B. As shown in figure 2, there was no significant difference between the two groups, with a 5-year DFS of 40.0% (CI95% 25.3 to 54.4) in group A and 43.0% (CI95% 24.3 to 60.4) in group B. Similar results were found in the multivariate analysis adjusted for prespecified confounders, with an adjusted HR of 1.03 (CI95% 0.50 to 2.13). Figure 2 presents DFS for each group.

Among the 27 patients who relapsed, 15 experienced local relapse (17.9%). Those included seven patients in group A (13.7%) and eight patients in group B (25.8%). The 5-year cumulative incidence of local relapse was 17.5% (CI95% 9.8 to 27.0) in the entire cohort, 13.0% (CI95% 5.2 to 24.5) in group A and 8.3% (CI95% 10.6 to 41.7) in group B (adjusted sHR=1.47, CI95% 0.31 to 7.07) (Figure 3).

Twelve patients (14.2%) presented nodal relapse. Those included eight patients in group A (15.7%) and four patients in group B (12.9%). Among these 12 patients, four didn't been treated by irradiation on draining lymph nodes. The 5-year cumulative incidence of nodal relapse was 16.0% (95%CI 8.7 to 25.2) in the entire cohort, 16.7% (95%CI 7.7 to 28.4) in group A and 14.9% (95%CI 4.5 to 31.3) in group B (adjusted sHR=0.72 (0.15 to 3.44)) (Supplemental figure 1).

Eighteen patients (21.4%) presented metastatic recurrences. Those included six patients in group A (11.3%) and 12 patients in group B (38.9%). The 5-year cumulative incidence of metastatic relapse was 21.6 (CI95%, 12.6 to 32.1) in the entire cohort, 11.1% (CI95% 4.0 to 22.4) in group A and 37.6% (CI95% 19.2 to 56.0) in group B (adjusted sHR=2.72, CI95% 0.48 to 15.24) (Supplemental figure 2).

Forty-eight patients (57.1%) died during the follow-up: 30 in group A (56.7%) and 18 in group B (58.1%). The 5-year OS was 50.7% (CI95% 38.2 to 62.0), with 50.8% in group A (CI95% 34.9 to 64.7) and 51.0% in group B (CI95% 30.4 to 68.4). There was no statistical difference between the overall survival rates in the two groups (adjusted HR=1.05 CI95% 0.42 to 2.61). OS according to the group is shown in *Figure 4*. 15 of those deaths (5 patients in group A (16.7%) and 9 patients in group B (50.0%)) were related to the MCC. The 5-year specific survival rate was 17.6% (CI95% 9.8 to 27.2): 10.6% (CI95% 3.8 to 21.4) in group A and 28.9% (CI95% 13.2 to 46.7) in group B. There was no statistical difference, in the adjusted model, between the specific survival rates in the two groups (sHR=7.16 CI95% 0.77 to 66.18) (*Supplemental figure 3*).

Irradiation dose:

In group A, seven out of 53 patients (13.2%) received an irradiation dose less than or equal to 45 Gy due to bad general conditions or to the occurrence of radiation-induced adverse events. With a median follow-up of 24 months, only one patient had a local relapse at 10 months of diagnosis and was treated successfully by surgery. Another patient had an early metastatic progression 3 months after the diagnosis.

Radiotherapy dose hypofractionation:

In group A, three patients (5.6%) were treated by hypofractionated RT in order to reduce the number of sessions and limit travels for their well-being. None of them had a local relapse. One of them had a nodal relapse at 6 months, which was controlled by subsequent RT. This patient died 10 years later from heart disease.

4. Discussion

Merkel cell carcinoma is a rare skin cancer, limiting the possibilities of large cohort studies. To our knowledge, we here report the largest case series on exclusive radiotherapy as a treatment strategy for MCC. Our study confirms that exclusive radiotherapy is an interesting alternative to surgery in localized MCC management.

The importance of adjuvant RT is now well known in the management of MCC. However, surgery is not always feasible in clinical routine due to anatomical issues or sequelae, especially in the head and neck region. Besides, old age and invasiveness of the surgical procedure are predictors of mortality in geriatric patients [16]. The risk of anesthesia-related mortality increases significantly in the elderly population [17]. In addition to the per-operative risks, post-operative confusion and post-operative cognitive dysfunction may occur, even after a minor surgery [18–20] Local anesthesia is sometimes not conceivable in view of

the complexity of the surgery, or in people with dementia. It remains a painful technique and may increase stress in some patients [21]. The elderly appear to be at a disproportionately increased risk for toxicity owing to the presence of relevant comorbidities and decreased muscle mass [22].

Our population is overall comparable to previously published data on MCC, on median age and median size of tumors [11–13]. As expected, the primitive tumor was frequently found in the cephalic region in our cohorts. This predominance is less underlined in other studies. Nevertheless, the distribution of primary tumor sites was not homogeneous in the two groups, with a clear predominance of cervicocephalic tumors in the RT monotherapy group (Group A). This result can be explained by a greater reluctance of clinicians to operate face-tumors due to risks of unaesthetic scars. Prognosis seems to be worse for head and neck tumors compared to limbs according to previous data[23], but despite a predominance of these lesions in the group A, no difference was found after adjustment on the localization.

We observed a 13.7%(95%CI 8.0-43.7) local recurrence rate in group A which is comparable to previously published studies [12,13]. Our results showed a 5-year OS of 50.8% (CI95% 34.9 to 64.7) in the RT monotherapy group, which is slightly higher than previously reported⁴³. Harrington *et al.*, report a 40.0% 5-year OS, but this study included a large proportion of stage III patients [13]. More patients in group B died from MCC (50%, compared to 16.0% in group A). All group A patients died from another cause (16 of them from organ failure, 2 of strokes, 1 of hematological disease and 1 of another solid cancer), which demonstrates that an overly aggressive approach is not necessary for localized MCC.

One of the strengths of our study was to choose exclusive RT strategy in patients with a tumor in place at the time of irradiation. Contrary to other studies, there was no resection even for cleanliness or debulking prior to irradiation. This approach was closer to clinical daily routine because of the difficult resection of these tumors. Furthermore, elderly people are characterized by a greater frailty, increasing their vulnerability to poor resolution of homoeostasis after a stress event. An apparently petty act (as minor surgery) could result in disproportionate changes in the health state [24]. Our study suggests that surgery could be avoided in some cases.

Limitations of our study are its monocentric and retrospective nature. In addition, we excluded a significant proportion of patients treated by surgery with insufficient margins.

Indeed, few patients were treated by RT and surgery with margins > 2cm. Still, the studies carried out in our center lead us to believe that RT is an essential step in the treatment of MCC. We believe that it is imperative not to delay the RT, and for this reason, we have reduced margins and promoted surgery allowing a direct suture, in order to obtain a rapid wound healing and early irradiation.

Four patients in our series had a SLNB, all in group B and with negative SLNB. This technique was not performed for MCC until 2010 and many patients treated by exclusive RT had contraindications to anaesthesia. Despite the risk of undiagnosed micrometastases in Group A patients, no difference was shown between the two groups.

Radiation dose was higher in group A than in group B.

In addition, none of the three patients who were treated by hypofractionated RT had a local relapse. Hypofractionated RT requires less hospital visits for patients compared to other techniques. It should nevertheless be reserved for elderly subjects, because it increases the risk of late toxicities.

Conclusions

Our findings suggest that exclusive radiotherapy is a promising treatment for early-stage MCC, even where the patients have not had prior surgery. This approach could be useful in elderly patients with comorbidities, or when surgery would cause significant functional or aesthetic sequelae.

Abbreviations

CNIL = Commission nationale Informatique et Libertés

DFS = Disease free survival

IQR = Interquartile range

MCPyV = Merkel cell polyomavirus

MCC = Merkel cell carcinoma

OS = Overall survival

RT = Radiotherapy

SLNB = Sentinel lymph node biopsy

Declarations

Conflicts of Interest in connection with this work: none

Ethical Approval and Consent to participate : All the patients of the study expressed their non-opposition to the use of their anonymized medical data. The study has been declared to and accepted by the CNIL

Consent for publication : All the patients of the study expressed their non-opposition to the use of their anonymized medical data. The study has been declared to and accepted by the CNIL

Availability of supporting data : All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Competing interests : None

Funding : None

Authors' contributions : M.D. and H.A. carried out the study. M.D. wrote the manuscript with support from H.A.,A.E. and F.De. X.M. and L.M. supervised the project. A.J. and F.Da. contributed to the data collection. M.K. and J.L. performed the analytic calculations. V.D. helped to the English translation.

Acknowledgements : None

References

- [1] Schadendorf D, Lebbé C, Zur Hausen A, Avril M-F, Hariharan S, Bharmal M, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. *Eur J Cancer* 2017;71:53–69. <https://doi.org/10.1016/j.ejca.2016.10.022>.
- [2] Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet* 2002;359:497–8. [https://doi.org/10.1016/S0140-6736\(02\)07668-7](https://doi.org/10.1016/S0140-6736(02)07668-7).
- [3] Rotondo JC, Bononi I, Puozzo A, Govoni M, Foschi V, Lanza G, et al. Merkel Cell Carcinomas Arising in Autoimmune Disease Affected Patients Treated with Biologic Drugs, Including Anti-TNF. *Clin Cancer Res* 2017;23:3929–34. <https://doi.org/10.1158/1078-0432.CCR-16-2899>.
- [4] Brewer JD, Shanafelt TD, Call TG, Cerhan JR, Roenigk RK, Weaver AL, et al. Increased incidence of malignant melanoma and other rare cutaneous cancers in the setting of chronic lymphocytic leukemia. *Int J Dermatol* 2015;54:e287-293. <https://doi.org/10.1111/ijd.12564>.
- [5] Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol* 2010;63:751–61. <https://doi.org/10.1016/j.jaad.2010.02.056>.
- [6] Tarantola TI, Vallow LA, Halyard MY, Weenig RH, Warschaw KE, Grotz TE, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. *J Am Acad Dermatol* 2013;68:425–32. <https://doi.org/10.1016/j.jaad.2012.09.036>.
- [7] Boccarda O, Girard C, Mortier L, Bens G, Saiag P, Guillot B. Guidelines for the diagnosis and treatment of Merkel cell carcinoma – Cutaneous Oncology Group of the French Society of Dermatology. *European Journal of Dermatology* 2012;22:375–9. <https://doi.org/10.1684/ejd.2012.1694>.
- [8] Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, et al. Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* 2018;16:742–74. <https://doi.org/10.6004/jnccn.2018.0055>.
- [9] Leonard JH, Ramsay JR, Kearsley JH, Birrell GW. Radiation sensitivity of Merkel cell carcinoma cell lines. *Int J Radiat Oncol Biol Phys* 1995;32:1401–7. [https://doi.org/10.1016/0360-3016\(94\)00610-W](https://doi.org/10.1016/0360-3016(94)00610-W).

- [10] Mortier L, Mirabel X, Fournier C, Piette F, Lartigau E. Radiotherapy alone for primary Merkel cell carcinoma. *Arch Dermatol* 2003;139:1587–90. <https://doi.org/10.1001/archderm.139.12.1587>.
- [11] Pape E, Rezvoy N, Penel N, Salleron J, Martinot V, Guerreschi P, et al. Radiotherapy alone for Merkel cell carcinoma: a comparative and retrospective study of 25 patients. *J Am Acad Dermatol* 2011;65:983–90. <https://doi.org/10.1016/j.jaad.2010.07.043>.
- [12] Veness M, Foote M, Gebiski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. *Int J Radiat Oncol Biol Phys* 2010;78:703–9. <https://doi.org/10.1016/j.ijrobp.2009.08.011>.
- [13] Harrington C, Kwan W. Outcomes of Merkel cell carcinoma treated with radiotherapy without radical surgical excision. *Ann Surg Oncol* 2014;21:3401–5. <https://doi.org/10.1245/s10434-014-3757-8>.
- [14] Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The Analysis of Failure Times in the Presence of Competing Risks. *Biometrics* 1978;34:541–54. <https://doi.org/10.2307/2530374>.
- [15] Schoenfeld D. Partial Residuals for The Proportional Hazards Regression Model. *Biometrika* 1982;69:239–41. <https://doi.org/10.2307/2335876>.
- [16] Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. *J Am Geriatr Soc* 2005;53:424–9. <https://doi.org/10.1111/j.1532-5415.2005.53159.x>.
- [17] Li G, Warner M, Lang BH, Huang L, Sun LS. Epidemiology of Anesthesia-related Mortality in the United States, 1999–2005. *Anesthesiology* 2009;110:759–65. <https://doi.org/10.1097/ALN.0b013e31819b5bdc>.
- [18] Shim JJ, Leung JM. An update on delirium in the postoperative setting: Prevention, diagnosis and management. *Best Practice & Research Clinical Anaesthesiology* 2012;26:327–43. <https://doi.org/10.1016/j.bpa.2012.08.003>.
- [19] N T, M B, V D, Li E, Jh K, Jm L, et al. Perioperative Cognitive Decline in the Aging Population. *Mayo Clinic Proceedings* 2011. <https://doi.org/10.4065/mcp.2011.0332>.
- [20] S N, J S, S H, S S, M M. Postoperative Cognitive Dysfunction After Noncardiac Surgery: A Systematic Review. *Anesthesiology* 2007. <https://doi.org/10.1097/0000542-200703000-00023>.
- [21] Bordianu A, Bobirca F. Facial skin cancer surgery under local anesthesia. *J Med Life* 2018;11:231–7. <https://doi.org/10.25122/jml-2018-0059>.
- [22] Waldinger R, Weinberg G, Gitman M. Local Anesthetic Toxicity in the Geriatric Population. *Drugs Aging* 2020;37:1–9. <https://doi.org/10.1007/s40266-019-00718-0>.

[23] Gb M, J M, Sd DS, Mp H, Am M, Mj B. Merkel Cell Carcinoma of the Head and Neck: Poorer Prognosis Than Non-Head and Neck Sites. *The Journal of Laryngology and Otology* 2016. <https://doi.org/10.1017/S0022215116000153>.

[24] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;381:752–62. [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9).

Table 1

Table 1: Baseline demographics and clinical characteristics of patients

n : number ; *y* : years ; Gy : Gray

TNM (tumor; nodes; metastatic) staging of Merkel Carcinoma in AJCC 8th Edition 2016

**Cumulative total dose*

	Overall patients n = 84	Exclusive RT (group A) n = 53	Surgery + RT (group B) n = 31	P value
Sex, n (%)				
Male	26 (31.0)	13 (24.5)	13 (41.9)	0.096
Female	58 (69.0)	40 (75.5)	18 (58.1)	
Median age, y (IQR)	79.0 (72.0 to 85.0)	82.0 (75.0 to 86.0)	77.0 (71.0 to 80.0)	0.022
Median size, mm (IQR)	25.0 (15.0 to 40.0)	20.0 (4.0-90.0)	25.0 (18.5-40.0)	0.17
Localization, n (%)				
Head and neck	50 (59.5)	43 (81.1)	7 (22.6)	<0.001
Limb	33 (39.3)	10 (18.9)	23 (74.2)	
Unknown	1 (1.2)	0 (0.0)	1 (3.2)	
Blood disease, n (%)	11 (13.1)	8 (15.1)	3 (9.6)	
TNM, n (%)	31 (36.9)	23 (43.3)	8 (25.8)	0.097
T1	36 (42.9)	19 (35.8)	17 (54.8)	
T2	14 (16.6)	11 (20.8)	3 (9.7)	
T3	3 (3.6)	0	3 (9.7)	
Unknown				
Median radiation dose on the lesion*, Gy, (IQR)	55.0 (50.0 to 62.0)	60.0 (50.0-65.0)	50.0 (50.0 to 54.0)	0.003
Median radiation dose on the draining lymph nodes, Gy, (IQR)	50.0 (40.0 to 50.0)	50.0 (33.0 to 50.0)	50.0 (50.0 to 55.0)	0.21

p-values are obtained using Chi-square tests for categorical characteristics and the Mann-Whitney U test for continuous characteristics.

Figures

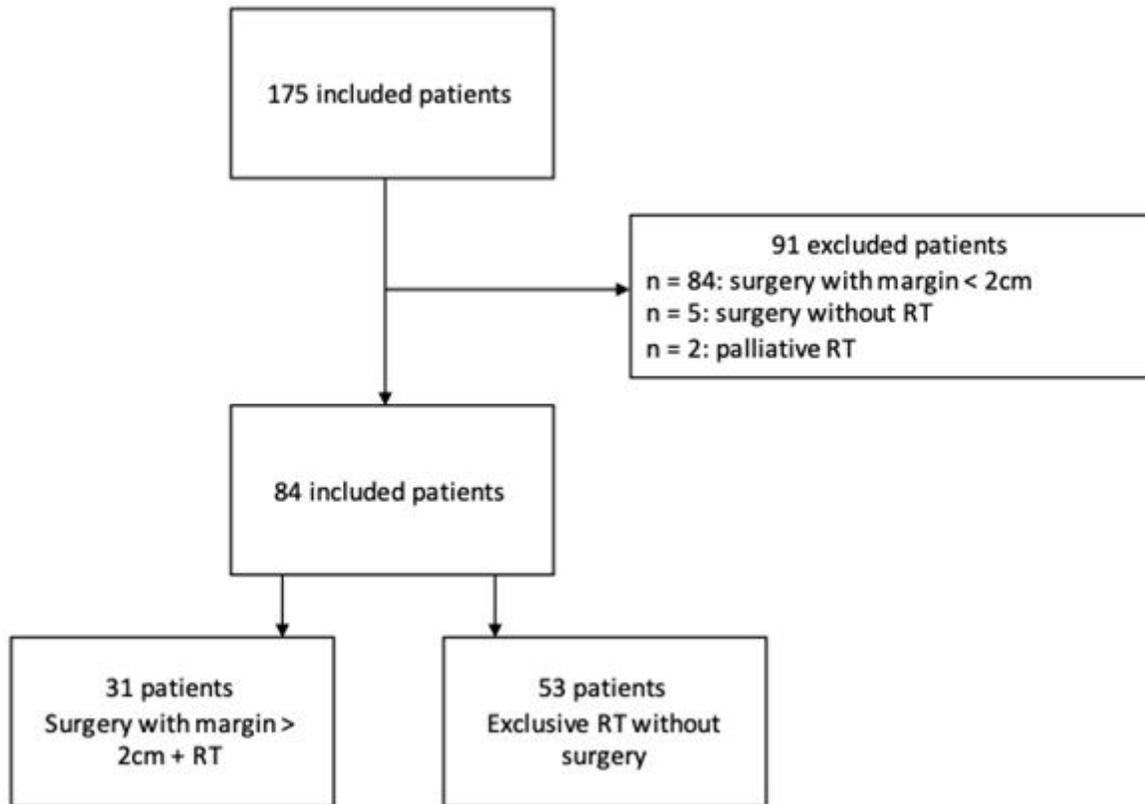
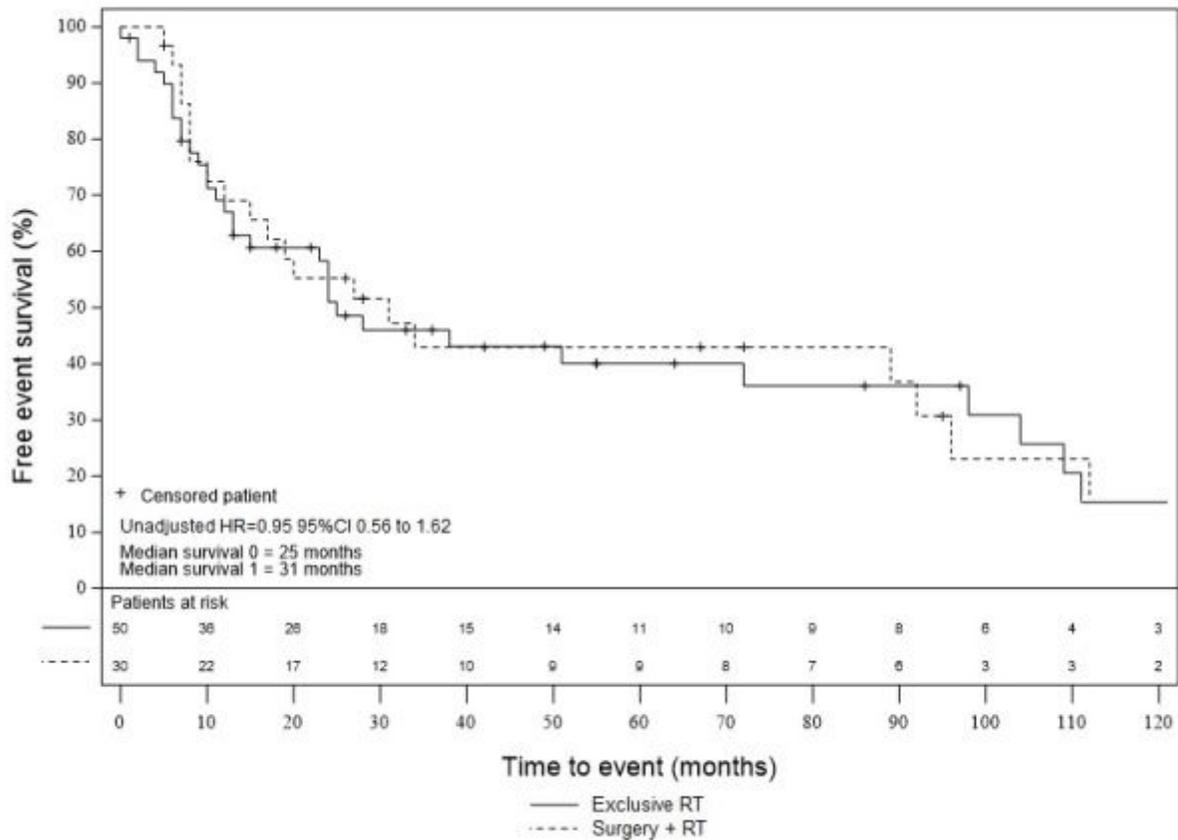


Figure 1

Study flow diagram

Survival curve



RT : external beam radiation therapy ; Group A = Exclusive RT ; Group B = Surgery + RT

Figure 2

Disease free survival (all relapses included) according to treatment group. There was no statistical difference, in the unadjusted (HR, 0.95, 95%CI 0.55 to 1.62) and adjusted model (HR=1.03 CI95% 0.50 to 2.13), between the disease free survival rates in the two groups using Cox regression models. The rates of overall survival were estimated using the Kaplan-Meier method.

Cumulative Incidence of local relapse

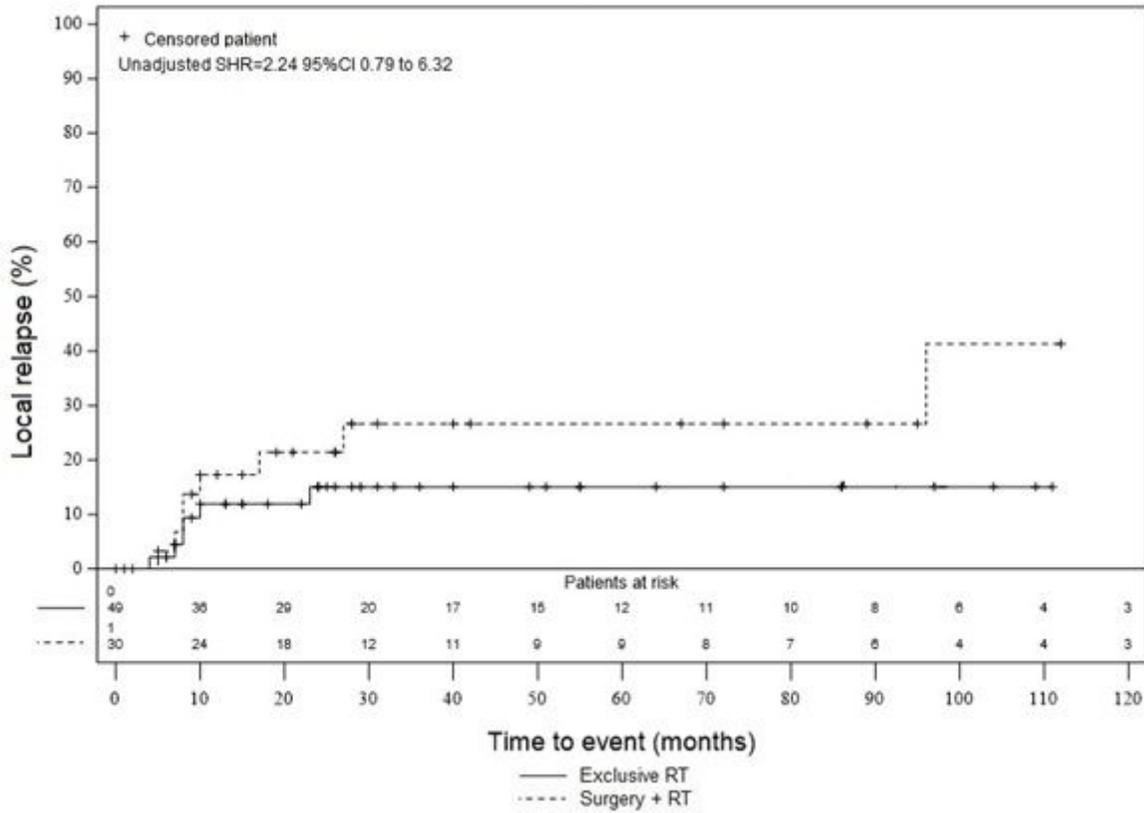
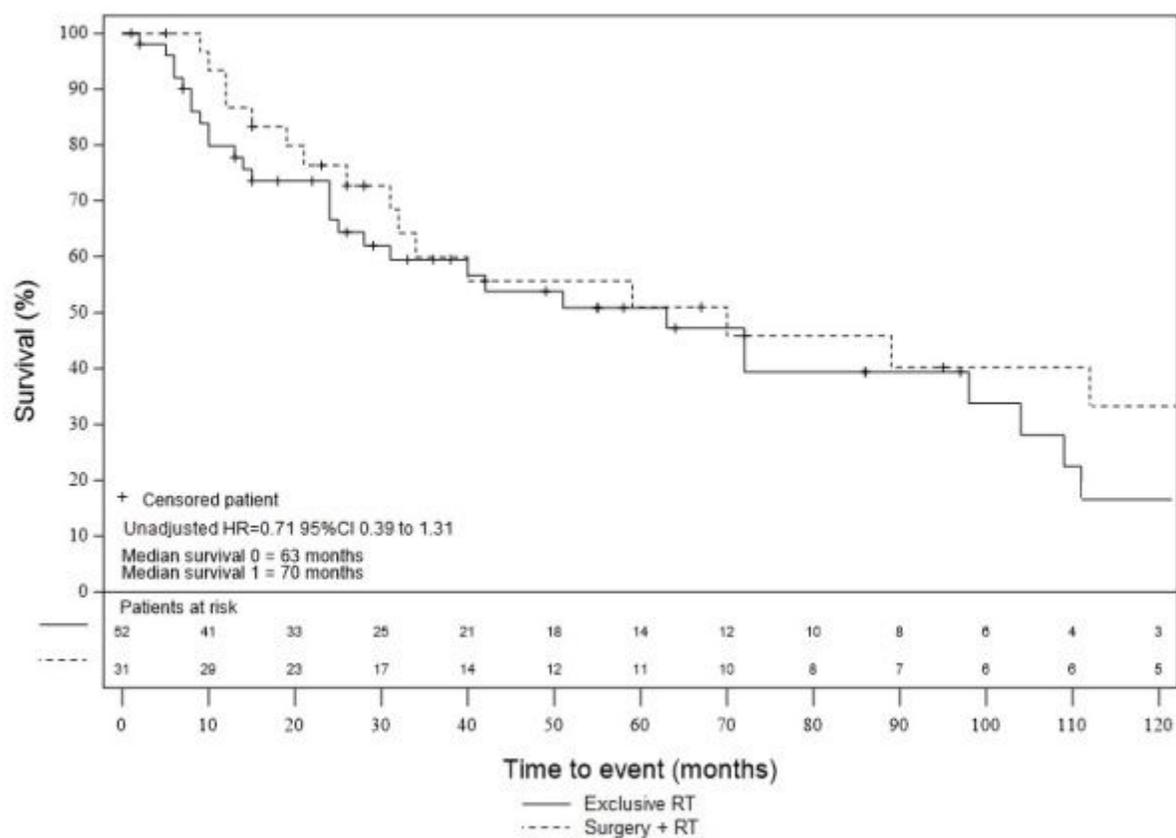


Figure 3

Cumulative incidence of local relapse according to treatment group. There was no statistical difference, in the unadjusted (sHR, 2.24, 95%CI 0.79 to 6.32) and adjusted model (sHR=1.47 CI95% 0.31 to 7.07), between the local relapse rates in the two groups using Fine-Gray models models. The rates of overall survival were estimated using the approach of Kalbfleisch and Prentice.

Survival curve



RT : external beam radiation therapy ; Group A = Exclusive RT ; Group B = Surgery + RT

Figure 4

Overall survival according to treatment group. There was no statistical difference, in the unadjusted (HR, 0.71, 95%CI 0.39 to 1.30) and adjusted model (HR=1.05 CI95% 0.42 to 2.61), between the overall survival rates in the two groups using Cox regression models. The rates of overall survival were estimated using the Kaplan-Meier method

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFigures.pdf](#)