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ORIGINAL ARTICLE

Regional nodal relapse in surgically staged Merkel cell carcinoma

Ulrike Hoeller · Thomas Mueller · Tina Schubert · Volker Budach · Pirus Ghadjar · Winfried Brenner · Felix Kiecker · Bernd Schicke · Oliver Haase

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Abstract
Purpose The nodal relapse pattern of surgically staged Merkel cell carcinoma (MCC) with/without elective nodal radiotherapy (RT) was studied in a single institution.
Method A total of 51 patients with MCC, 33% UICC stage I, 14% II, 53% III (4 lymph node metastases of unknown primary) were eligible. All patients had surgical staging: 23 patients sentinel node biopsy (SNB), 22 patients SNB followed by lymphadenectomy (LAD) and 6 patients LAD. In all, 94% of the primary tumors (PT) were completely resected; 57% of patients received RT, 51% of known PT sites, 33% (8/24 patients) regional RT to snN0 nodes and 68% (17/27 patients) to pN+ nodes, mean reference dose 51.5 and 50 Gy, respectively. Mean follow-up was 6 years (range 2–14 years).
Results A total of 22% (11/51) patients developed regional relapses (RR); the 5-year RR rate was 27%. In snN0 sites (stage I/II), relapse occurred in 5 of 14 nonirradiated vs. none of 8 irradiated sites ($p=0.054$), resulting in a 5-year RR rate of 33% versus 0% ($p=0.16$). The crude RR rate was lower in stage I (12%, 2/17 patients) than for stage II (43%, 3/7 patients). In stage III (pN+), RR appeared to be less frequent in irradiated sites (18%, 3/14 patients) compared with nonirradiated sites (33%, 3/10 patients, $p=0.45$) with 5-year RR rates of 23% vs. 34%, respectively.
Discussion Our data suggest that adjuvant nodal RT plays a major role even if the sentinel nodes were negative.
Conclusion Adjuvant RT of the lymph nodes in patients with stage IIa tumors and RT after LAD in stage III tumors is proposed and should be evaluated prospectively.

Keywords Skin neoplasms · Lymph nodes · Radiotherapy · Biopsy · Lymphadenectomy

U. Hoeller, M.D. (✉) · T. Mueller · T. Schubert, M.D. ·
Prof. Dr. med. V. Budach, M.D. · Priv.Doz.
Dr. med. P. Ghadjar, M.D.
Department of Radiation Oncology,
Charité Universitätsmedizin Berlin,
Charitéplatz 1,
10117 Berlin, Germany
e-mail: Ulrike.hoeller@charite.de

Prof. Dr. med. W. Brenner, M.D.
Department of Nuclear Medicine, Charité Universitätsmedizin Berlin,
Berlin, Germany

Dr. med. F. Kiecker, M.D.
Department of Dermatology, Charité Universitätsmedizin Berlin,
Berlin, Germany

B. Schicke
Tumor Center Berlin,
Berlin, Germany

Dr. med. O. Haase, M.D.
Department of Surgery, Charité Universitätsmedizin Berlin,
Berlin, Germany

Regionäre Rezidive bei Merkelzell-Karzinom nach chirurgischer Stadienbestimmung

Zusammenfassung
Ziel Untersucht wurde das regionäre Rezidivmuster des Merkelzell-Karzinoms (MCC) nach chirurgischem Staging und stadienadaptierter Therapie.
Methode und Patienten Eingeschlossen wurden 51 Patienten mit lokalisiertem MCC: 33% hatten UICC-Stadium-I-, 14% -II-, 53% -III-Tumoren (davon 4 Lymphknotenmetastasen eines unbekannten Primärtumors). Alle Patienten erhielten ein chirurgisches Staging: 23 Wächterlymphkno-

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tenbiopsien (SNB), 22 SNB gefolgt von Lymphadenektomie (LAD) und 6 LAD. Vollständig reseziert waren 94 % der Primärtumoren (PT). Eine Radiotherapie (RT) erhielten 57 % der Patienten, 51 % eine RT der PT-Region, 33 % (8/24) eine regionäre RT bei snN0 und 68 % (17/27) auf pN+ mit einer mittleren Gesamtdosis von 51,5 bzw. 50 Gy. Die mittlere Nachbeobachtungszeit lebender Patienten betrug 6 Jahre (Spanne 2–14).

Ergebnisse Insgesamt 22 % (11/51) entwickelten ein regionäres Rezidiv (RR), die 5-Jahres-RR-Rate betrug 27 %, die krude RR-Rate 31 % (8/26) der nichtbestrahlten vs. 12 % (3/25) der bestrahlten Patienten (p = 0,1). Im Stadium I/II (snN0) traten Rezidive in 5 von 14 unbestrahlten und in 0 von 8 bestrahlten Regionen auf (p = 0,054, 5-Jahres-RR-Rate 33 vs. 0 %, p = 0,16). Die krude RR-Rate war im Stadium I (12 %, 2/17) niedriger als im Stadium II (43 %, 3/7). Im Stadium III (pN+) traten weniger RR nach Bestrahlung auf (18 %, 3/14, in bestrahlten vs. 33 %, 3/10, in unbestrahlten Regionen, p = 0,45) entsprechend 5-Jahres-RR-Raten 23 vs. 34 %.

Diskussion Die regionäre Rezidivrate ist auch bei sN0 ohne adjuvante RT hoch und wird durch die RT reduziert.

Schlussfolgerung Die adjuvante regionäre RT von Lymphknoten bei Patienten mit Stadium IIa (snN0) sowie nach LAD im Stadium III erscheint sinnvoll und sollte prospektiv evaluiert werden.

Schlüsselwörter Kutane Tumoren · Lymphknoten · Strahlentherapie · Biopsie · Lymphadenektomie

Merkel cell carcinoma (MCC) is a rare aggressive cutaneous tumor. Locoregional relapse occurs in up to 55–64 % of all patients [1]. Regional relapse rates (RR rate) range from 8–37 % [2, 11, 13, 16, 18, 19, 21, 38]. In-transit metastases in the cutaneous draining lymph channels are well known but rarely evaluated [9, 17, 36]. Some retrospective studies and one randomized study have consistently shown that radiotherapy (RT) of the primary tumor region significantly reduces the local relapse rate and may improve overall survival [11, 16, 18, 21, 26]. Chemotherapy is under investigation [14, 23, 28]. Recently, the prognostic value of surgical nodal staging was described [20]. German guidelines recommend complete excision of the primary tumor and adjuvant RT of the tumor bed, surgical nodal staging in clinically node-negative patients and lymphadenectomy of metastatic nodal regions [4].

However, adjuvant RT of regional lymphatic nodes remains controversial. We studied the nodal relapse pattern of patients treated at our institution for surgically staged MCC.

Material and methods

Patients

Fifty-one patients of a total of 61 patients referred between 1998 and 2011 with localized MCC underwent surgical nodal staging and were included in this study. Staging included computed tomography (CT) of the chest, CT neck in case of primary tumor (PT) in the head and neck and CT or sonography of upper abdomen and sonography of nodal basins relevant to PT site.

The institutional treatment policy was excision biopsy of the primary tumor, re-excision with margins of ≥2 cm, in the head and neck for functional reasons ≥1 cm. Sentinel node biopsy (SNB) was performed and completed by radical lymphadenectomy (LAD) of the affected regional basin if nodal metastases were found. In case of palpable lymph nodes, upfront LAD was recommended.

Sentinel node procedure

^{99m}Tc nanocolloid (Nanocoll, Amersham, GE Healthcare) was injected intracutaneously at either side of the scar. Lymphoscintigraphy was performed according to the respective procedure guideline [39] in the dynamic acquisition mode starting immediately after tracer injection until each visualized lymph channel reached an endpoint, i.e., its putative lymph node. Lymph channels and nodes were marked on the skin.

During biopsy, the sentinel node was identified with a hand-held gamma probe. In addition, patent blue dye was injected to facilitate the localization of the respective nodes as previously described [22].

The sentinel nodes were completely cross-sectioned, HE- and immune-stained for cytokeratin 20 (CK-20).

Nodal surgery

Surgery was executed by surgeons experienced in melanoma surgery. In a review of surgical notes and histology reports, O.H. (author) classified nodal surgery as SNB only, single lymph node excision, regional resection, or radical resection of the nodal basin.

Radiotherapy

Adjuvant RT was initiated as soon as possible after completion of wound healing. RT of the primary tumor bed including all scars and metastases containing draining nodal basins was indicated. RT of pathologically uninvolved nodal regions was at the discretion of the radiation oncologist; radiation of involved nodes was indicated. Treatment plans were reviewed by U.H. and T.M. with regard to treatment

volume (PT, probable in-transit-region, regional nodes) and dose applied (intended and incidental).

Follow-up

Seventeen patients were followed prospectively. Charts of the remaining 34 patients were checked and treating physicians interviewed. Living patients were invited for a follow-up visit and, if unable to attend the clinic, interviewed by phone. The site of locoregional relapse (LRR) was identified from charts and related to the treatment plans. Relapse was defined as local (LR, within approximately 5 cm of the scar of the PT or 2 cm of skin graft), in-transit (IT, the region of draining intracutaneous lymph channels between PT and first or second order lymph nodes), regional (RR, first or second order lymph nodes), and distant metastases. In-field relapse was defined as in field, marginal (tumor mass approximately within 2 cm of field margin) and out of field.

Statistics

Tumors were re-classified according to UICC. Stage I a/b is defined by pT1 N0, stage II a/b by pT2–3 N0, "a" by pathological and "b" by clinical nodal staging, IIC by T4N0, stage III by any T pN1, "a" by micrometastases and "b" by macrometastases.

The statistics are descriptive. For group comparisons c^2 and Fisher's exact test were used for categorical and continuous variables, respectively. A P value < 0.05 was considered statistically significant. Actuarial locoregional relapse (LRR rate, i.e. local and/or IT and/or regional relapse), local relapse rate (LR rate), regional relapse rate (RR rate) were calculated according to the Kaplan–Meier method from the day of complete resection of the primary to first relapse or the last follow up information, not censoring for distant metastases. Comparisons were made with log rank test. Overall survival was calculated for last follow-up information or death of any cause. Statistical package SPSS 21 was used.

The false negative rate was calculated as nodal recurrence/false negative plus true positive (i.e. SNB-proven metastases).

Results

Patient characteristics

Of the 61 patients referred for treatment of PT, 51 patients had surgical nodal staging. The male to female ratio was 1:1.2, and the mean age was 68 years (range 51–89 years). The most frequent PT sites were the upper limb (21 patients), lower limb (12 patients), and head and neck (9 patients).

Table 1 Patient and treatment characteristics

		Patients n (%) $N=51$
Site of PT	Upper limb	21 (41)
	Lower limb	12 (23)
	Head and neck	9 (18)
	Torso	5 (10)
	Unknown primary	4 (8)
Tumor stage	I	17 (33)
	II	7 (14)
	III	27 (53)
Surgery of PT	Complete resection of PT	44 (94)[a]
	Incomplete resection of PT	2 (4)
	Unknown resection status of PT	1 (2)
Surgery of nodes	Sentinel node biopsy only (SNB)	23 (45)
	Up-front LAD[b]	6 (12)
	SNB plus LAD	22 (43)
	Number of removed nodes (LAD)	Mean 17 (range 4–71)
Radio-therapy	Dose to PT tumor bed	Mean 51.5 Gy (range 38–71)
	Dose to nodal basin	Mean 50 Gy (range 40–60)
	Intentional dose to in transit region	Mean 50.4 (range 50–50.4)

PT primary tumor, *LAD* lymphadenectomy

[a]Total 47 patients plus 4 unknown primaries

[b]Including 4 patients with lymph node metastases of unknown primary and 2 patients with pN+

Four patients had occult primaries (Table 1). Seventeen patients (33 %) had a stage I tumor, 7 (14 %) stage II, and 27 (53 %) stage III tumor, respectively.

Treatment

Surgery

Complete resection of the primary tumor was achieved in the majority of patients (44 of 47 patients with known primary), resection with close/involved margins in two and not defined in one patient. All clinically node negative patients referred for treatment of known primaries had a sentinel node biopsy, detection rate 100 %. Two patients (pN+) as well as the four patients with clinical nodal metastases of unknown primaries had up-front LAD. All but one of 21 patients with positive sentinel nodes (and two patients with snN0) had complete LAD. Lymphadenectomy was radical in the majority of the cases (25 pN+ patients, 21 radical, 4 regional procedures).

Radiotherapy

Twenty-nine patients (57%) were referred for RT. Reasons for omitting RT were high age and frailty, co-morbidity, or very delayed wound healing. RT started within a mean of 7.8 weeks (range 1.7–17.8 weeks) after completion of surgery. The PT region was treated with electrons of adequate energy using bolus material. The technique for nodal treatment varied according to the anatomic location of PT and nodal basins. The regional nodes in limbs and torso were treated with 6 MV/15 MV photons either with opposing fields or with CT-based conformal therapy. Tumors in the head and neck region were treated with IMRT for the regional nodes, either including the PT region or with an additional electron field to the PT region to minimize toxicity [5, 37].

A total of 61% (29 of 47) known primary sites were irradiated. A mean reference dose of 51.5 Gy (range 38–71 Gy) was applied in 5 weekly fractions of 1.8–2 Gy. Prescription dose was generally 50–50.4 Gy. Three PT regions were boosted to 60–71 Gy. Two patients discontinued radiation because of toxicity and patient refusal, respectively.

In all, 49% (25/51) patients received nodal irradiation; 33% (8/24) vs. 63% (17/27 patients) of node negative vs. positive nodal regions, respectively, were irradiated. The mean reference dose was 50.7 Gy (range 40–60 Gy).

The probable IT regions were irradiated incidentally in 6 patients with approximately 30–40 Gy. Intentional treatment was given to three IT regions with 50 Gy in all cases.

Chemotherapy was not used. The mean follow-up for living patients was 6 years (range 2–14 years).

For treatment details refer to Table 1.

Treatment results

Sixteen locoregional relapses occurred. Only one relapse was observed more than 2 years after treatment; the 5-year locoregional relapse rate was 46%. Five patients had isolated distant metastases as first recurrence. Seventeen patients died; the 5-year overall survival was 72%.

Nodal relapse

Of the locoregional relapses, 69% (11/16) occurred in the nodes. The actuarial 5-year RR rate was 27%, stage-adapted 18% stage I, 46% stage II and 27% stage III, p=0.079. Crude RR rate was 31% (8/26 patients) in nonirradiated vs. 12% (3/25 patients) in irradiated sites (p=0.1), 5-year RR rate, 0.35 vs. 0.26% p=0.19 (Figs. 1 and 2).

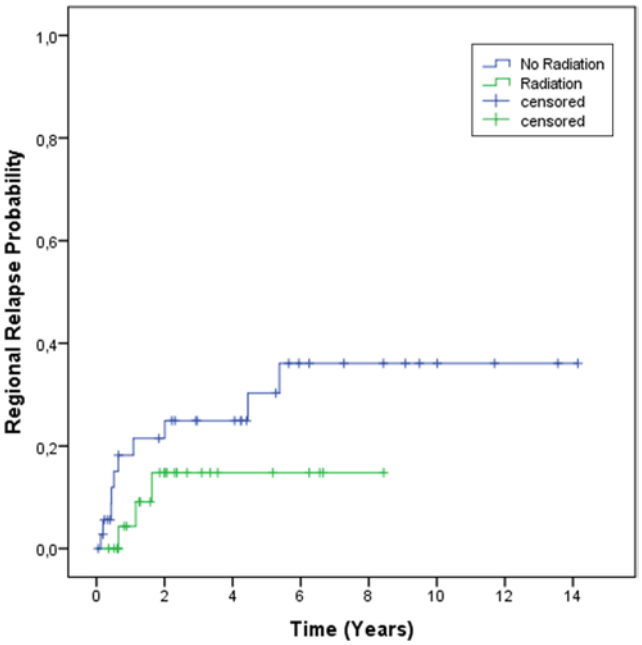

Fig. 1 Regional relapse rate in patients with/without radiation: 51 patients at risk, 26 patients without radiation (RT), 25 patients with RT. The 5-year RR rate 0.35 vs. 0.26%, p=0.19

Node-negative patients

A crude RR rate of 36% was observed in nonirradiated snN0sites (5/14 patients), compared to 0% in irradiated sites (0/8 patients), p=0.054 (Fig. 2). The corresponding 5-year RR rates were 33 vs. 0%, respectively (p=0.16, Fig. 3).The risk of relapse in snN0 sites seems to be related to tumor size, the crude RR rate for T1 tumors was 12% (2/17 patients) versus 43% (3/7 patients) for T2 tumors. The actuarial 5-year RR rates were 23 versus 46% (p=0.166). Taking irradiation into account, regional relapse occurred in stage I in 0/5 irradiated sites versus 2/12 nonirradiated sites, in stage II in 0/3 irradiated versus 3/4 nonirradiated sites (Table 2).

The false-negative rate was 19% (5 nodal recurrences/5 nodal recurrences snN0 plus 21 snN+).

Node-positive patients

Despite radical clearance of all sites with macroscopic metastases and of all snN+ sites but one, elective radiation was prescribed in the majority of patients (68%) by the treating radiation-oncologist (Fig. 2). The crude RR rate was 22% and the 5-year RR rate was 37%. The crude RR rate was 18% (3/14 patients) in irradiated versus 30% (3/10 patients) in nonirradiated sites (p=0.46). The corresponding 5-year RR rates were 23 versus 34% (p=0.46).

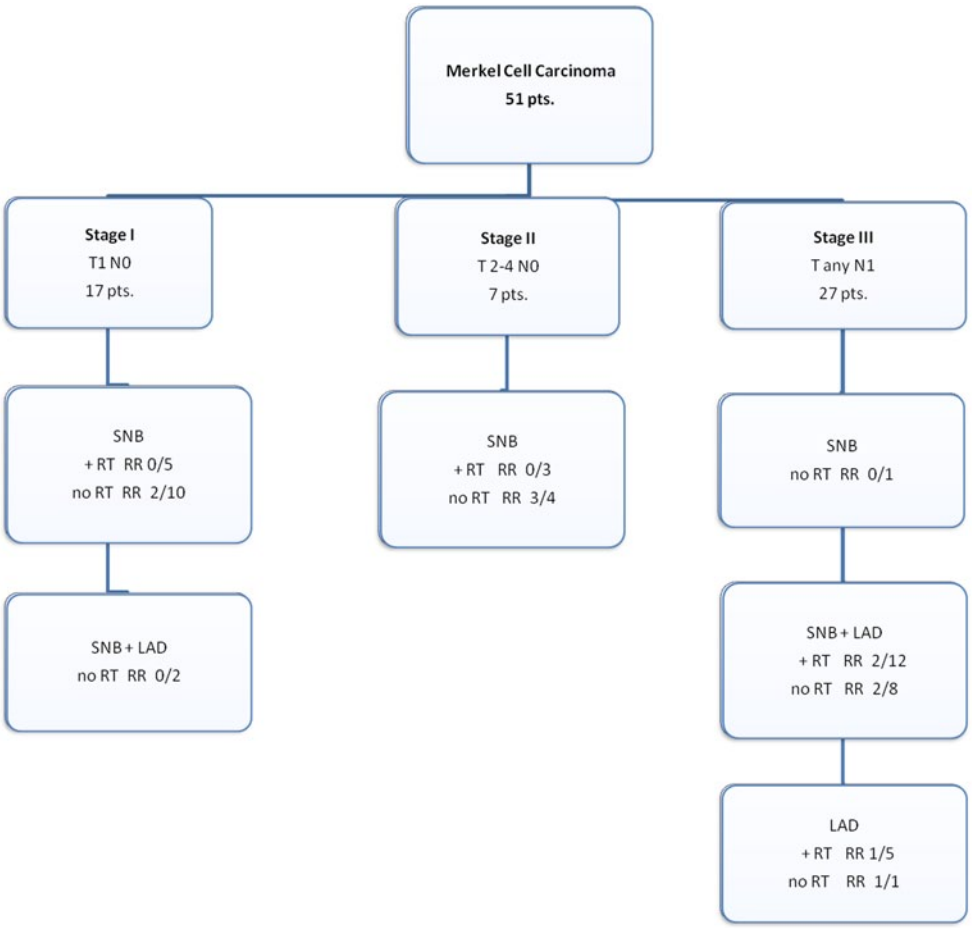

Fig. 2 Overview of staging procedures, treatment of draining nodal basins and the resulting regional relapse. *RT* radiotherapy of regional nodes, *RR* regional relapse, *SNB* sentinel node biopsy, LAD lymphadenectomy, *pts* patients

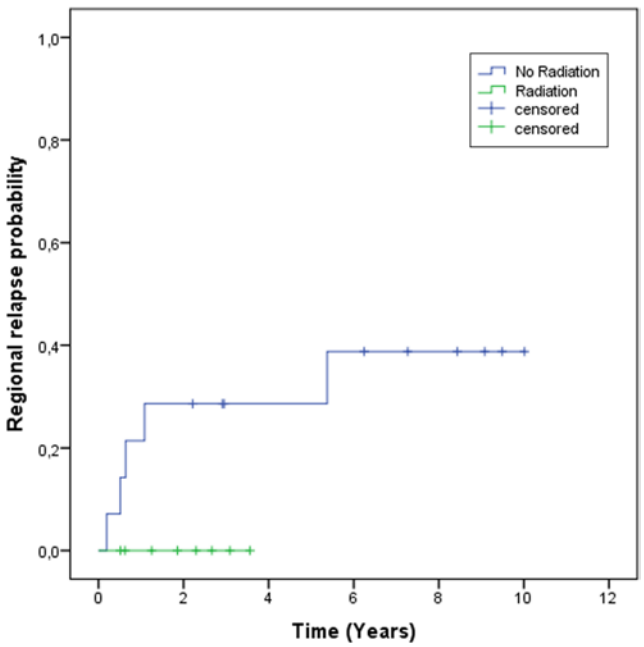

Fig. 3 Regional relapse rate in patients with stage I/II (snN0) with/without radiation: 22 patients at risk, 14 patients without RT, 8 patients with RT. The 5-year RR rate 0 vs. 33 %, The difference was not significant (p = 0.13)

Discussion

In this single institution study, results of surgically staged patients with/without elective RT of nodal basins are presented. In contrast to register studies or compilations of literature data, relapse patterns were analyzed with respect to RT volume and total dose.

In snN0 sites (stage I/II), relapse occurred in 5 of 14 non-irradiated versus none of 8 irradiated sites (p = 0.054), corresponding to a 5-year RR rate of 33 % versus 0 % (p = 0.16). In stage III (pN+), RR appeared to be less frequent in irradiated sites (18 %, 3/14 patients) compared with nonirradiated sites (33 %, 3/10 patients, p = 0.45) leading to a 5-year RR rate of 23 versus 34 % respectively.

Treatment concepts for MCC have evolved from excision of primary tumor and overt lymph node metastases to wide excision or Mohs micrographic tumor resection and systematic adjuvant RT of the primary tumor bed. Currently, the approach for lymph node staging and treatment is under debate. Lymph node metastases are a strong negative prognostic factor for overall survival [20, 23]. Accurate nodal staging has a major impact on prognosis in MCC. In a cohort study on 2856 patients [6], clinically node nega-

Table 2 Nodal relapse in relation to size of primary tumor and adjuvant radiation therapy (*RT*) in patients stage I and II (snN0) with sentinel node biopsy only. χ^2 $p=0.076$

		Nodal relapse	No nodal relapse	Sum
T1 Tumor <2 cm	No RT of nodal basins	2	8	10
	RT of nodal basins	0	5	5
T1 Tumor >2 cm	No RT of nodal basins	3	1	4
	RT of nodal basins	0	3	3
Sum		5	17	22

tive patients had a shorter survival time relative to an age-matched cohort than patients with pathologically proven negative nodes (excess hazard ratio 1.8, p<0.001). The optimal management of nodal basins, especially the role of elective RT, is currently not well defined.

Sentinel node-negative patients

Current recommendations range from no nodal staging for tumors smaller than ≤1 cm [34] to elective RT for all patients [10]. Sentinel node biopsy detected metastases in 15–47% of patients with tumors ≤1 cm [2, 3, 7–9, 13, 30, 32]. This compares to the high rate of regional relapse of 16–37% described in a systematic literature review of clinically node-negative patients [21]. Sentinel node biopsy is increasingly used. However, there is limited evidence on regional recurrence in snN0 sites (overview in Table 3) [3, 8, 13, 15, 22, 30].

In our institution, SNB for MCC was implemented in 1998 [21]. The outcome of 22 patients with SNB proven negative nodes is reported with respect to elective therapy. The crude incidence of 31% regional recurrences and 70% 3-year RR free survival is in line with the largest reported series that report 10% [7] and 20% crude incidence [12], respectively, and 80% 3-year RR free survival [12].

SNB was introduced although, to our knowledge, the false-negative rate of this procedure has not been verified by systematic radical LAD in snN0 patients as e.g. in breast cancer [11]. Fields et al. [7] calculated a false-negative rate of 15% in their series [i.e., nodal recurrence/false negative + true positive (i.e., SNB-proven metastases]. In this study, the false-negative rate was 19%. It should be considered an approximation because the rate is highly influenced by the base line proportion of nodal metastases in a given population. The calculation cannot substitute a formal validation of SNB accuracy.

Elective treatment of N0 sites, LAD [25] or radiation [6, 12, 16, 25, 28, 30, 31] is used inconsistently and some publications do not allow correlation of elective therapy and outcome [25, 31]. RT volumes, especially local vs. locoregional, are frequently not specified [20, 23]. Also in our institution, RT of nodes was not indicated consistently. Reasons for omitting RT were frailty of patients or prolonged wound healing. In three patients, reasons could not be identified retrospectively. This does not influence results. In our study, there was a surprisingly high rate of 36% regional recurrences in nonirradiated nodal regions (5 of 14 patients) in contrast to no relapse in electively radiated sites (0 of 8 patients) resulting in a 5-year RR-free survival of 60 vs. 100%, respectively. The difference did not quite reach significance (p=0.054), most probably due to the small sample size. A similar observation was reported by Gupta et al. [12], who found a 3-year RR-free survival of 90% with vs. 70% without elective RT (n.s., p=0.26), suggesting a benefit of elective nodal therapy. In contrast, in a larger series on 99 patients without elective RT, the crude nodal relapse rate was 8% [7]. An overview of the cases reported to date is given in Table 3. In conclusion, elective RT of nodes should be considered in high risk patients. Based on our results, we advocate regional irradiation in patients with stage IIa tumors and after LAD in stage III tumors. The effectiveness of RT was clearly demonstrated in a randomized study on clinical node negative patients [17]. Elective radiation of nodal regions vs. observation resulted in 0 vs. 16.7% regional relapses (p=0.007).

If risk features for nodal relapse were defined, treatment could be adapted to the individual risk profile. Size of primary tumor >2 cm showed an insignificant trend for nodal recurrence in the largest series [7], in contrast to a smaller series of compiled data [12]. In our series, there was a trend to higher rates of nodal relapse in patients with T2 tumors; however, the number of patients is small. Fields et al. [7] describe a significant association of lymphovascular invasion of the primary tumor with detection of sentinel node metastases and with nodal/distant recurrence.

Sentinel node-positive patients

Due to the fortunately small number of patients with positive sentinel nodes, there is even less evidence for adjuvant therapy. Taking into account the higher recurrence rates and lower disease-free survival, therapy is usually more aggressive, i.e., complete LAD without or with adjuvant radiotherapy is frequently employed. Our results of 5-year RR rates without/with radiation of 35 vs. 23% compare with a report on 3-year RR rate of 100 vs. 40% without/with RT [12], nonsignificant due to small patient numbers. Recently, a series on 50 patients suggested that local radiation is equieffective to LAD with/without RT for nonpalpable disease [5].

Table 3 Overview of original reports on outcome of patients with sentinel node biopsy proven negative nodes (stage Ia/IIa). Reports with less than 5 patients or no information on follow up time excluded. Elective therapy was given as stated.

	Patients	Relapse patients	Elective therapy patients	Follow-up mean, months
Ortin-Perez 2007 [27]	5	0	0	57
Hui 2011 [17]	5	0/4 RT 0/1 no RT	4 RT	47
Migliano 2009 [25]	5	0	0	Range 22–72
Warner 2008 [40]	8	0/2 RT 5/6 no RT	2 RT	Median 16
Messina 1997 [24]	10	0	0	"Medium" 10, maximum 26
Hill 1999 [15]	16	0	0	7
Allen 1999 [2]	19	1	Unknown	19
Su 2002 [35]	6	0/1 RT 0/5 no RT	1 RT	19
Alex 2004 [1]	5	0/5	0	20 (range 11–29)
Sexton 2013 [33]	26	3/26*	4 RT	36
Fields 2012 [9]	108	3/9 RT 8/99 no RT	9 RT	Median 42
Santamaria-Barria 2013 [29]	18	7/12* SNB or LAD	RT details not available	Median 36
Bajetta 2009 [3]	13	Crude cumulative incidence 17%	0	Median 65
Tarantola 2012 [36]	42	3 year RRFS† 82%*	Use of RT and RT volume not detailed for SNB patients	40
Gupta 2006 [13]	20	1/14** 2/6**	14 RT 6 no RT	2–45
Schmalbach 2005 [31]	8	1	0	34
This study	22	0/8 5/14	8 RT 14 no RT	72

RT radiotherapy *LAD* lymphadenectomy *SNB* sentinel node biopsy *RRFS* regional relapse free survival

*relation to regional RT vs. no regional RT is not available

** lymph node recurrence or metastases, site not stated

†RRFS regional relapse free survival

Conclusion

RT is highly effective in MCC. Our data suggest that adjuvant nodal RT plays a major role even if the sentinel nodes were negative. Currently, we suggest regional RT in patients with stage IIa tumors and after LAD in stage III tumors. This approach will have to be validated by a larger set of patients.

Compliance with ethical guidelines

Conflict of interest U. Hoeller, T. Mueller, T. Schubert, V. Budach, P. Ghadjar, W. Brenner, F. Kiecker, B. Schicke, and O. Haase state that there are no conflicts of interest.

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