

1 Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous
2 squamous cell carcinoma with clear histologic margins

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4 Emily Stamell Ruiz, MD, MPH^{*}; Shlomo A. Koyfman, MD[†]; Syril Keena T. Que, MD, MPH[‡];
5 Jason Kass, MD, PhD[‡]; Chrysalyne D. Schmults, MD, MSCE^{*}

6
7 ^{*}*Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School,*
8 *Boston, MA*

9 [‡]*Department of Dermatology, Indiana University School of Medicine, Indianapolis, IN*

10 [†]*Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH*

11 [‡]*Department of Otolaryngology, Brigham and Women's Hospital, Harvard Medical School,*
12 *Boston, MA*

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29 **Reprint requests:** Chrysalyne Schmults

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31 **Corresponding Author:**

32 Chrysalyne D. Schmults, MD, MSCE

33 Department of Dermatology, Brigham and Women's Hospital

34 1153 Centre Street Suite 4J, Boston, MA 02130

35 Tel.: 617-983-4626 | Fax: 617-983-4504 | Email: cschmults@partners.org

36

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37 **Abbreviations:**

38	AJCC	American Joint Committee on Cancer
39	BWH	Brigham and Women's Hospital
40	CCPDMA	Complete Circumferential Peripheral and Deep Margin Assessment
41	CSCC	Cutaneous Squamous Cell Carcinoma
42	DM	Distant Metastasis
43	DSD	Disease-Specific Death
44	LCNI	Large Caliber Nerve Invasion
45	LR	Local Recurrence
46	LVI	Lymphovascular Invasion
47	MMS	Mohs Micrographic Surgery
48	NCCN	National Comprehensive Cancer Network
49	NM	Nodal Metastasis
50	PNI	Perineural Invasion
51	S+ART	Surgery and Adjuvant Radiation
52	SM	Surgery Monotherapy
53		

54 **Abstract**

55 **Background:** Though NCCN recommends consideration of localized adjuvant radiation
56 following clear-margin surgery for cutaneous squamous cell carcinoma (CSCC) with large
57 caliber (≥ 0.1 mm) nerve invasion (LCNI) and other high-risk features, only a single small study
58 has compared surgery plus adjuvant radiation (S+ART) to surgical monotherapy (SM) for
59 CSCC.

60 **Objectives:** Compare surgery plus adjuvant radiation (S+ART) to surgical monotherapy (SM)
61 for primary CSCCs with LCNI and other risk factors.

62 **Methods:** Matched retrospective cohort study of primary CSCCs (matched on gender, age,
63 immune status, type of surgery, diameter, differentiation, depth and LCNI) treated with S+ART
64 versus SM. Subgroup analysis of CSCCs with LCNI was performed.

65 **Results:** 62 CSCCs were included in matched analysis (S + ART: 31, SM: 31) and 33 in LCNI
66 analysis (S+ART: 16, SM: 17). There was no significant difference in local recurrence (LR),
67 metastasis, or death from disease in either analysis. Risk of LR was low (7, 8%) with 3 of the
68 LRs being effectively treated upon recurrence.

69 **Limitations:** Single academic center, non-randomized design.

70 **Conclusion:** Adjuvant radiation did not improve outcomes compared to SM due to a low
71 baseline risk of recurrence; although ART for named nerve invasion and LCNI of 3 or more
72 nerves has been shown to improve outcomes in a prior study. Randomized studies are needed to
73 define the subset of CSCC for whom adjuvant radiation has utility.

74

75 **Introduction**

76 Approximately 3.7-5.2% of CSCCs will develop metastasis and 2-3.5% of patients will die from
77 disease.¹⁻⁴ While the primary treatment of high-risk tumors is surgical removal with complete
78 circumferential peripheral and deep margin assessment (CCPDMA), adjuvant therapies are
79 sometimes considered in cases thought to have a risk of recurrence or death.⁵ Adjuvant
80 radiation (ART) is sometimes used following surgery with clear histologic margins for
81 select cases of CSCC. The National Comprehensive Cancer Network (NCCN) includes ART as
82 a consideration for margin-negative CSCCs with extensive, large (nerve caliber $\geq 0.1\text{mm}$), or
83 named-nerve involvement or if other high-risk features are present at the clinician's
84 discretion.⁵

85

86 Despite these recommendations, data on the efficacy of ART for margin-negative CSCCs is
87 limited. Prior studies have focused on CSCCs with perineural invasion (PNI); however, the
88 majority do not compare radiation outcomes to tumors treated with surgery monotherapy (SM)
89 and so the effect of radiation is difficult to quantify.⁶⁻¹¹ One prior study of 102 tumors that
90 compared S+ART to SM found longer recurrence- (94% vs. 25%, $p=0.01$) and disease-free (73%
91 vs. 40%, $p=0.05$) 2-year survival in tumors with PNI of more than 2 nerves ($n=30$), respectively,
92 but there was no difference in cases with PNI of 1-2 nerves.¹² Whether tumors had clear surgical
93 margins prior to radiation was not specified.

94

95 Data on ART for high-risk CSCCs without PNI is very heterogenous due to lack of consensus on
96 the definition of high-risk CSCC. A 2009 systematic review was unable to draw conclusions
97 about ART efficacy due to insufficient data.¹³ A more recent analysis evaluated local recurrence
98 (LR) following ART for 52 high-risk CSCCs with depth of invasion > 6mm or desmoplasia.
99 While the study excluded gross residual tumor post-surgery, it included tumors with
100 histologically positive margins (n=16). LR-free survival was 96% (95% confidence interval, 90-
101 100%) at 2 years but there was no SM group for comparison.¹⁴

102

103 Radiation therapy is associated with morbidity, high-cost, and can complicate future attempts at
104 resection should recurrence occur. Thus, data evaluating its impact on outcomes in the adjuvant
105 setting for node-negative CSCC is needed in order to utilize radiation appropriately. The aim of
106 this study was to perform a matched analysis of the impact of ART on completely-resected
107 primary CSCC. Since large-caliber (≥ 0.1 mm in caliber) nerve invasion (LCNI) is an indication
108 to consider ART per NCCN guidelines and there is data to support improved outcomes in tumors
109 with LCNI, but not small caliber PNI,^{5,12} a subgroup analysis of cases with LCNI was also
110 performed utilizing controls without PNI.

111

112 **Methods**

113 ***Data Collection***

114 The study was approved by Partners Human Research Committee. Patients with CSCC
115 diagnosed at Brigham and Women's Hospital (BWH) from 1/1/2000-12/31/2017 were identified
116 via department of pathology electronic database. Pathology reports were reviewed and

117 noncutaneous SCC, anogenital SCC, in situ CSCC, and recurrent CSCC were excluded. Medical
118 records of all eligible patients were reviewed for primary tumor data, outcome data [including
119 local recurrence (LR), nodal metastasis (NM), distant metastasis (DM), and disease-specific
120 death (DSD)], and types of treatment performed (including surgical approach and adjuvant
121 therapy). Cases that received localized radiation underwent additional chart review for the
122 following information: radiation modality, dose, fractions, dates that treatment was performed,
123 and reason for ART. Only primary tumors with clear histologic margins following surgical
124 excision (either wide local excision or Mohs micrographic surgery (MMS)) were included.

125

126 ***Matched Analysis***

127 Primary tumors treated with surgical excision with clear surgical margins and ART (S+ART)
128 were identified. Exact matching was used to select tumors treated with surgical excision
129 monotherapy with clear surgical margins (SM). Case pairs were matched on gender, age (+/- 10
130 years), immune status, type of surgical treatment, diameter (≥ 2 cm vs. <2 cm), differentiation
131 (poor vs. well or moderate), depth of invasion (beyond subcutaneous fat vs.
132 dermis/subcutaneous fat), and LCNI (present vs. absent). Tumors where controls could not
133 be identified were excluded from analysis.

134

135 ***Large Caliber Nerve Invasion (LCNI) Analysis***

136 Since LCNI is the most common indication for ART and a number of these tumors treated with
137 ART could not be matched due to the strict matching criteria, LCNI tumors were analyzed
138 separately. All primary LCNI tumors with surgically clear margins were included in this

139 analysis, stratified by whether ART was used (including 6 cases contained in the matched
140 analysis above).

141

142 *Statistical Analyses*

143 Patient and tumor characteristics were analyzed using descriptive statistics and frequency
144 tabulation. For the matched analysis, outcomes of interest were analyzed by tumor pair and
145 McNemar's Test was used to determine whether there was a difference in LR, NM, DM. For the
146 LCNI cohort analysis, Chi-square and Fisher's exact tests were used to determine whether there
147 was a difference in LR, NM, DM, and DSD. Multivariable and survival analyses were not
148 performed due to small number of outcomes and lack of significance on univariate analysis.

149

150 All reported p -values were two-sided with type I error (α) of <0.05 considered to be statistically
151 significant. Statistical analyses were performed using Stata version 14.0 (StataCorp, College
152 Station, TX).

153

154 **Results**

155 *Matched Case Analysis*

156 Forty-one CSCCs treated with surgical excision with clear margins and ART were identified of
157 which 31 were able to be matched to similar cases as per criteria described in methods (table 1).
158 There was no statistical difference in gender, age, immune status, diameter, depth of invasion,
159 large caliber PNI, differentiation, type of surgical treatment (i.e. excision vs. MMS), and tumor
160 location in S+ART vs. SM groups. Details on the patient and tumor risk factors for cases in the
161 S+ART group are included in table 5. Although it did not meet statistical significance, more

162 tumors in the radiation group had lymphovascular invasion (LVI; S+ART 4 (13%) vs. SM 1
163 (3%), $p=0.4$). There was a statistically significant difference in median follow-up time (S+ART
164 49.5 (SD 32.8) vs. SM 32.9 (SD 27.3), $p=0.03$). Based on the American Joint Committee on
165 Cancer (AJCC) 8th edition staging system for CSCC of the head and neck, there was no
166 difference in tumor stages. The majority of tumors in both groups were BWH T2b (S+ART 20
167 (65%) vs. SM 21 (68%)).

168
169 In the S+ART group, the reason for radiation included perineural invasion (9, 29%), multifocal
170 infiltrative tumor (9, 29%), deeply invasive tumor to bone, cartilage, parotid, or fascia (8, 26%),
171 lymphovascular invasion (4, 13%), and no epidermal connection (1, 3%). Details of the radiation
172 treatment were available for 28 (90%) patients with all receiving localized radiation only.
173 Twenty-seven (96%) patients completed their planned radiation treatment which ranged from 39-
174 70 Gy total. Three patients received chemoradiation consisting of cisplatin (dose not available) in
175 1 patient. The other two received carboplatin 1-1.5auc + paclitaxel 30mg/m² for 2 and 4 weeks
176 during the course of ART. One of the patients discontinued the chemotherapy due to
177 hospitalization and one switched to cetuximab 250mg/m² for 1 week due to pancytopenia. In
178 terms of acute radiation toxicities, most patients experienced grade 1 or 2 skin erythema. One
179 (3%) experienced grade 3 skin erythema and 4 (13%) experienced grade 1 or 2 mucositis. Two
180 patients developed late radiation toxicities; 1 (3%) had recurrent cellulitis and 1 (3%) had
181 chronic pain.

182
183 Clinical outcomes for the matched-case analysis are shown in table 3. A total of 4 tumors
184 developed poor outcomes (LR (1), NM (1), LR+DSD (1), LR+DM+DSD (1)). There was no

185 difference in LR (S+ART 3 (10%) vs. SM 1 (3%), $p=0.3$), NM (S+ART 1 (3%) vs. SM 0 (0),
186 $p=0.3$), DM (S+ART 1 (3%) vs. SM 0 (0), $p=0.3$), and DSD (S+ART 2 (6%) vs. SM 0 (0),
187 $p=0.2$). Of the 3 LRs in the S+ART cohort, 1 was treated with MMS and had no further
188 recurrences after 84 months of follow up, 1 patient developed an inoperable recurrence on the
189 scalp and died of local disease 6 weeks after diagnosis of the recurrence, and 1 patient developed
190 an LRs on the scalp as well as in transit metastases, NM, and DM and died of disease 5 months
191 after diagnosis of the recurrence. The LR in the SM cohort was treated with a WLE with a
192 positive deep margin and salvage radiation. The patient developed NM and DM 9 months later
193 and died of disease 11 months after diagnosis of the recurrence. Of note, one patient in the
194 S+ART group died from a second primary CSCC (not part of the study) diagnosed 6 years after
195 the study tumor and did not receive radiation. The study tumor had no evidence of recurrence 81
196 months after diagnosis when the patient died of the other CSCC so the study tumor was recorded
197 as no LR, NM, or DSD.

198

199 *LCNI Analysis*

200 Thirty-three tumors were included in the LCNI analysis, of which 16 (48%) received S+ART
201 and 17 underwent SM (52%) (table 2). There was no difference in follow up time,
202 immunosuppression, tumor location, tumor diameter, depth of invasion, histologic
203 differentiation, LVI, primary tumor treatment, adjuvant chemotherapy, or AJCC 8 tumor stage.
204 The SM was 10 years older and 40% more male than the S+ART group, though these were not
205 statistically significant differences between the groups. There was a statistically significant
206 difference in tumor stage by the BWH staging system with low stage tumors (BWH T2a)

207 comprising 41% of the SM group and 0% of the S+ART group ($p=0.01$). Thus, all cases in the
208 S+ART group had another prognostic risk factor besides LCNI.

209

210 Table 3 includes the clinical outcomes for the LCNI analysis based on treatment. A total of 3
211 tumors developed poor outcomes (LR (2), LR+DSD (1)). Although there was no statistically
212 significant difference in any outcome, more cases in the SM group had LRs [S+ART 0 (0) vs.
213 SM 3 (18%), $p=0.2$]. One of the 3 patients developed multiple in transit metastases treated with
214 excision and ART, with no evidence of recurrence at 9 months. The second patient developed a
215 LR requiring orbital exenteration. A second recurrence was treated with palliative radiation, and
216 resulted in death shortly thereafter. The final patient had a LR successfully treated with MMS
217 with no evidence of recurrence 36 months later.

218

219 *Description of Cases with Poor Outcomes*

220 Table 4 summarizes the characteristics and outcomes of the cases with poor outcomes in both the
221 matched case and LCNI analyses.

222

223 **Discussion**

224 To the best of our knowledge, this study is the first to compare S+ART to SM for node-negative
225 primary CSCCs with clear surgical margins, the second for cases with PNI, the first for cases
226 with LCNI, and the first to conduct a matched analysis of multiple prognostic factors. There was
227 no difference in outcomes in either the matched-case or LCNI analyses. The results are in
228 keeping with the other study of PNI in that a (non-significant) trend was found for less LR in
229 cases with significant (large-caliber) PNI treated with ART. However, 2 of the 3 LRs in the SM

230 group accounting for the trend were effectively treated at the time of LR. In the 89 total cases
231 reported herein, only 7 (8%) had a local recurrence, of which 3 were successfully salvaged at the
232 time of LR. The null findings herein reflect a low baseline risk of poor outcomes for high-stage
233 primary CSCCs with clear histologic margins. Even when LR occurs, most patients still appear
234 to be curable. Although this is a small study, a post-hoc power analysis shows that the matched
235 analysis was adequately powered to detect a 50% reduction in LR, the effect of ART on
236 recurrence rates in epithelioid tumors, since the sample size needed is 53 total tumors and the
237 analysis include 62 tumors. The LCNI analysis was powered to detect a 60% reduction, so a
238 larger study is needed to assess smaller reductions.

239

240 Margin status following surgery greatly impacts outcomes. CCPDMA (en face sectioning with
241 nearly 100% margin assessment, e.g. Mohs excision) is recommended by the NCCN for high-
242 risk CSCCs (as is wide excision if it can be closed primarily).¹⁵ A systematic review comparing
243 standard assessment (approximately 1% of margin histologically evaluated) to CCPDMA found
244 a higher risk of recurrence for keratinocytic carcinomas with PNI treated with standard
245 assessment (23%) versus CCPDMA (10%, $p=0.0004$).¹⁶ A recent study of 647 CSCCs treated
246 with only MMS found that 10%, 17%, 5%, and 5% of 145 high-stage CSCCs (defined as BWH
247 T2b/T3) the risk of LR was only 10%.¹⁷ ART for epithelial tumors is offered when the risk of
248 recurrence exceeds 15-20%. Since radiation is not expected to impact nodal or distant metastasis,
249 a 10% LR risk for high-stage CSCC may not be high enough for radiation to significantly impact
250 recurrence risk.

251

252 It is possible that if a subset of CSCCs with a greater risk of LR were identified, radiation may be
253 better able to influence outcomes. Meanwhile, since the risk of poor outcomes is elevated for
254 high-stage CSCC, it is reasonable to monitor such tumors with close clinical and radiologic
255 surveillance.^{18,19} Though the data presented herein do not support ART solely on the basis of
256 PNI, none of the cases had named nerve and extensive PNI was not routinely recorded given the
257 lack of a clear definition. Therefore, it is possible that ART may impact outcomes with more
258 extensive nerve invasion. Currently in our practice, we utilize ART for named nerve invasion,
259 LCNI with 3 or more nerves, as supported by the single comparative study of more advanced
260 PNI,¹² or when clear surgical margins are in question. A multidisciplinary discussion is
261 recommended for very aggressive or recurrent tumors in order to select cases that may benefit
262 from adjuvant treatment.

263
264 Despite the findings presented herein, it is important to recognize that there is good evidence to
265 support radiation for node-positive CSCCs. A retrospective study of 122 patients with CSCCs
266 metastatic to cervical lymph nodes found improved 5-year disease free survival (74% vs. 34%,
267 $p=0.001$) and 5-year overall survival (66% vs. 27%, $p=0.003$) in patients who underwent surgery
268 and radiation compared to surgery alone.²⁰ Another study found lower locoregional recurrence
269 (20% vs. 43%, p values not reported) and improved 5-year disease-free survival rate (73% vs.
270 54%; $p=0.004$) in 167 patients with metastatic CSCC of the head and neck (including parotid
271 metastases) who received S+ART versus SM, respectively.²¹

272
273 This study is subject to limitations. In the matched-case analysis, the shorter mean follow-up
274 time in SM group (SM 33 months vs. S+ART 49 months) could underestimated the risk of

275 poor outcomes. However, average follow up time was more than 2 years and 85-96% of
276 recurrences occur within 2 years of treatment, so the impact of the differential follow-up
277 was likely minimal.^{12,22} Since the study is retrospective, there were no standard inclusion
278 criteria for tumors receiving ART. However, the cohort reflects current clinical scenarios where
279 ART is utilized in CSCC. Radiation treatment fields were not reviewed and there was
280 variation in treatment protocols. However, in the matched analysis there was only 1 LR in
281 the SM group indicating surgery alone may be sufficient, which would make variation in
282 radiation protocols a moot point. In the LCNI analysis, those in the surgical monotherapy
283 group were 10 years older and 40% more male (both are factors associated with worse
284 CSCC outcomes).²³ However, this group also had lower stage disease (41% were BWH low-
285 stage vs none in ART group). Such differences likely balanced each other and are unlikely
286 to be responsible for the lack of difference seen between treatment groups.

287
288

289 **Conclusion**

290 ART for node- and margin-negative primary CSCC did not improve outcomes compared to SM,
291 due to low baseline risk of poor outcomes in primary CSCCs with clear histologic margins. The
292 18% local recurrence risk in LCNI cases treated with SM is relatively high, but represents only 3
293 cases of recurrence, 2 of which were successfully treated at time of recurrence. Randomized
294 trials are needed to define which CSCC patients benefit from ART. Meanwhile, the present
295 study represents the only comparative study of ART versus SM for node- and margin-negative
296 CSCCs.

297

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306 **References**

- 307 1. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated
308 incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J
309 Am Acad Dermatol 2013;68:957-66.
- 310 2. Eigentler TK, Leiter U, Hafner HM, Garbe C, Rocken M, Breuninger H. Survival of
311 Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study. J
312 Invest Dermatol 2017;137:2309-15.
- 313 3. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining
314 prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol
315 2008;9:713-20.
- 316 4. Mourouzis C, Boynton A, Grant J, et al. Cutaneous head and neck SCCs and risk of
317 nodal metastasis - UK experience. J Craniomaxillofac Surg 2009;37:443-7.
- 318 5. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology:
319 Squamous Cell Skin Cancer. Version 2.2019. Available from URL:
320 https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed March
321 14, 2019.
- 322 6. Warren TA, Panizza B, Porceddu SV, et al. Outcomes after surgery and postoperative
323 radiotherapy for perineural spread of head and neck cutaneous squamous cell carcinoma.
324 Head Neck 2016;38:824-31.
- 325 7. Erkan S, Savundra JM, Wood B, Acharya AN, Rajan GP. Clinical perineural invasion of
326 the trigeminal and facial nerves in cutaneous head and neck squamous cell carcinoma:
327 Outcomes and prognostic implications of multimodality and salvage treatment. Head Neck
328 2017;39:1280-6.

- 329 8. Lin C, Tripcony L, Keller J, Poulsen M, Dickie G. Cutaneous carcinoma of the head and
330 neck with clinical features of perineural infiltration treated with radiotherapy. *Clin Oncol*
331 *(R Coll Radiol)* 2013;25:362-7.
- 332 9. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in
333 cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head*
334 *Neck* 2009;31:604-10.
- 335 10. McCord MW, Mendenhall WM, Parsons JT, Flowers FP. Skin cancer of the head and
336 neck with incidental microscopic perineural invasion. *Int J Radiat Oncol Biol Phys*
337 1999;43:591-5.
- 338 11. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous cell
339 carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys*
340 2012;82:334-40.
- 341 12. Sapir E, Tolpadi A, McHugh J, et al. Skin cancer of the head and neck with gross or
342 microscopic perineural involvement: Patterns of failure. *Radiother Oncol* 2016;120:81-6.
- 343 13. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical
344 monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous
345 cell carcinoma: a systematic review of outcomes. *Dermatol Surg* 2009;35:574-85.
- 346 14. Yan BY, Kim SK, Ma J, Barker CA. Local recurrence and quality of life after adjuvant
347 radiation therapy in high-risk squamous cell carcinoma. *Br J Dermatol* 2018.
- 348 15. Davis R, Loescher LJ, Rogers J, et al. Evaluation of Project Students are Sun Safe
349 (SASS): A University Student-Delivered Skin Cancer Prevention Program for Schools. *J*
350 *Cancer Educ* 2015;30:736-42.

- 351 16. Fraga SD, Besaw RJ, Schmults CD, Kass JI, Piris A, Waldman A. Complete Marginal
352 Assessment versus Sectional Assessment in Surgically Excised Keratinocytic Carcinoma.
353 Under Review. .
- 354 17. Marrazzo G, Zitelli JA, Brodland D. Clinical outcomes in high-risk squamous cell
355 carcinoma patients treated with Mohs micrographic surgery alone. *J Am Acad Dermatol*
356 2018.
- 357 18. Fox M, Brown M, Golda N, et al. Nodal Staging of High Risk Cutaneous Squamous Cell
358 Carcinoma. *J Am Acad Dermatol* 2018.
- 359 19. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic
360 imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad*
361 *Dermatol* 2017;76:217-25.
- 362 20. Wang JT, Palme CE, Morgan GJ, GebSKI V, Wang AY, Veness MJ. Predictors of outcome
363 in patients with metastatic cutaneous head and neck squamous cell carcinoma involving
364 cervical lymph nodes: Improved survival with the addition of adjuvant radiotherapy. *Head*
365 *Neck* 2012;34:1524-8.
- 366 21. Veness MJ, Morgan GJ, Palme CE, GebSKI V. Surgery and adjuvant radiotherapy in
367 patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph
368 nodes: combined treatment should be considered best practice. *Laryngoscope*
369 2005;115:870-5.
- 370 22. Khan K, Mykula R, Kerstein R, et al. A 5-year follow-up study of 633 cutaneous SCC
371 excisions: Rates of local recurrence and lymph node metastasis. *J Plast Reconstr Aesthet*
372 *Surg* 2018;71:1153-8.

- 373 23. Duran J, Morgan FC, Karia PS, Schmults CD. An evaluation of high-stage cutaneous
374 squamous cell carcinoma outcomes by sex. *Br J Dermatol* 2017;177:1131-3.

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Table 1. Baseline characteristics of cases in the matched-case analysis

Characteristics	Surgical monotherapy (n=31)	Surgery + ART (n=31)	p-value*
Age at diagnosis, mean (SD), y	73.9 (11.9)	69.1 (12.8)	0.1 [†]
Follow-up time, median (IQR), months	32.9 (27.3)	49.5 (32.8)	0.03 [†]
Sex, n (%)			
Female	9 (29)	9 (29)	1.0
Male	22 (71)	22 (71)	
Immunosuppression, n (%)			
No	18 (58)	21 (68)	0.6
Yes	13 (42)	10 (32)	
Tumor location, n (%)			
Ear and lip	5 (16)	7 (23)	0.6
Head and neck	19 (61)	18 (58)	
Trunk	4 (13)	4 (13)	
Arms, hands, legs, feet	3 (10)	2 (6)	
Tumor diameter			
<2.0 cm	12 (39)	12 (39)	1.0
≥2.0 cm	19 (61)	19 (61)	
Depth of invasion			
Dermis/Subcutaneous fat	14 (45)	14 (45)	1.0
Beyond Subcutaneous fat	17 (55)	17 (55)	
Histologic differentiation			
Well and moderate	15 (48)	15 (48)	1.0
Poor	16 (52)	16 (52)	
Perineural invasion			
No	20 (65)	13 (42)	0.1
Yes	11 (35)	18 (58)	
Diameter of perineural invasion			
<0.1 mm or no perineural invasion	25 (81)	25 (81)	1.0
≥0.1 mm	6 (19)	6 (19)	
LVI			
No	30 (97)	27 (87)	0.4
Yes	1 (3)	4 (13)	
Primary treatment, n (%)			
Surgical excision	9 (29)	10 (32)	1.0
Mohs surgery	22 (71)	21 (68)	
Adjuvant chemotherapy			
No	31 (100)	28 (90)	0.2 [‡]
Yes	0 (0)	3 (10)	
AJCC-8 tumor stage			
T1	5 (16)	3 (10)	0.9
T2	2 (6)	1 (3)	
T3	16 (52)	20 (65)	
T4	1 (3)	1 (3)	
Not applicable [§]	7 (23)	6 (19)	

BWH tumor stage			
T1	0 (0)	0 (0)	
T2a	9 (29)	7 (23)	0.4
T2b	21 (68)	20 (65)	
T3	1 (3)	4 (13)	
Indication for ART			
Perineural invasion	-	9 (29)	NA
Multifocal infiltrative Tumor	-	9 (29)	
Deeply invasive to bone, cartilage, parotid, or fascia	-	8 (26)	
Lymphovascular invasion	-	4 (13)	
No epidermal connection	-	1 (3)	

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; SD, standard deviation; ART, adjuvant radiation therapy.

*Chi-square statistics unless otherwise specified

§AJCC-8 staging only applies to CSCC on the head and neck. "Not applicable" indicates tumors on non-head and neck locations.

†Student t-test p-value

‡Fisher exact test p-value

Table 2. Baseline characteristics of cases with large caliber nerve invasion (LCNI)

Characteristics	Surgical monotherapy (n=17)	Surgery + ART (n=16)	p-value*
Age at diagnosis, mean (SD), y	73.5 (15.2)	63.8 (16.7)	0.09 [†]
Follow-up time, median (IQR), months	27.3 (21.6)	43.3 (30.9)	0.09 [†]
Sex, n (%)			
Female	5 (29)	9 (56)	0.2
Male	12 (71)	7 (44)	
Immunosuppression, n (%)			
No	9 (53)	11 (69)	0.5
Yes	8 (47)	5 (31)	
Tumor location, n (%)			
Ear and lip	1 (6)	4 (25)	0.5
Head and neck	12 (71)	10 (63)	
Trunk	2 (12)	1 (6)	
Arms, hands, legs, feet	2 (12)	1 (6)	
Tumor diameter			
<2.0 cm	12 (71)	8 (50)	0.3
≥2.0 cm	5 (29)	8 (50)	
Depth of invasion			
Dermis/Subcutaneous fat	9 (53)	7 (44)	0.7
Beyond Subcutaneous fat	8 (47)	9 (56)	
Histologic differentiation			
Well and moderate	16 (94)	12 (75)	0.2
Poor	1 (6)	4 (25)	
LVI			
No	17 (100)	16 (100)	1.0
Yes	0 (0)	0 (0)	
Primary treatment, n (%)			
Surgical excision	0 (0)	0 (0)	1.0
Mohs surgery	17 (100)	16 (100)	
Adjuvant chemotherapy			
No	17 (100)	16 (100)	1.0 [‡]
Yes	0 (0)	0 (0)	
AJCC-8 tumor stage			
T1	0 (0)	0 (0)	0.7
T2	0 (0)	0 (0)	
T3	13 (76)	14 (88)	
T4	0 (0)	0 (0)	
Not applicable [§]	4 (24)	2 (12)	
BWH tumor stage			
T1	0 (0)	0 (0)	0.01
T2a	7 (41)	0 (0)	
T2b	10 (59)	15 (94)	
T3	0 (0)	1 (6)	

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; SD, standard deviation; PNI, perineural invasion; ART, adjuvant radiation therapy

*Chi-square statistics unless otherwise specified

§AJCC-8 staging only applies to CSCC on the head and neck. "Not applicable" indicates tumors on non-head and neck locations.

†Student t-test p-value

‡Fisher exact test p-value

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Table 3. Clinical outcomes

Matched-Case Tumors			
	Surgical monotherapy (n=31)	Surgery + ART (n=31)	p-value*
Local recurrence, n (%)	1 (3)	3 (10)	0.3
Nodal metastases, n (%)	0 (0)	1 (3)	0.3
Distant metastases, n (%)	0 (0)	1 (3)	0.3
Disease-specific death, n (%)	0 (0)	2 (6)	0.2
Large Caliber PNI Tumors			
	Surgical monotherapy (n=17)	Surgery + ART (n=16)	p-value†
Local recurrence, n (%)	3 (18)	0 (0)	0.2
Nodal metastases, n (%)	0 (0)	0 (0)	1.0
Distant metastases, n (%)	0 (0)	0 (0)	1.0
Disease-specific death, n (%)	1 (6)	0 (0)	1.0

Abbreviations: ART, adjuvant radiation therapy; PNI, perineural invasion

*p-value determined using McNemar's Test

†p-value determined using Fisher's Exact Test

Table 4. Characteristics and outcomes of cases from the matched-case and LCNI analyses which developed a poor outcome.

Case #	Clinical History	Tumor Location	Tumor Stage (BWH/AJCC 8)	High-Risk Factors	Primary Tumor Treatment	Outcomes	Disease Free Survival (months)
Poor Outcomes from Case-Control Analysis							
1	82-year-old M Diffuse large T cell lymphoma	Cheek	T2B/T3	Poor-Differentiation Tumor Diameter (3.0cm) Depth of invasion (fascia)	MMS	LR	3
<i>Matched Case Treated with S+ART</i>	75-year-old M CLL	Scalp	T3/T3	Poor-Differentiation Tumor Diameter (4.0cm) Depth of invasion (bone)	MMS ART with electrons (55Gy in 20 fractions)		81
2	42-year-old M Kidney Transplant	Cheek	T2B/T3	Tumor Diameter (4.0cm) Depth of Invasion (Parotid)	MMS ART (60Gy in 30 fractions)	LR	8
<i>Matched Case Treated with SM</i>	64-year-old M Lung Transplant	Ear	T2B/T3	Tumor Diameter (2.5cm) Depth of Invasion (Perichondrium)	MMS		69
3	74-year-old M Lung Transplant	Scalp	T2B/T3	Poor-Differentiation Depth of Invasion (fascia) LVI	MMS ART with electrons (60Gy in 30 fractions)	LR DM DSD	5
<i>Matched Case Treated with SM</i>	77-year-old M	Scalp	T2B/T3	Poor-Differentiation Depth of Invasion (Fascia)	MMS		25
4	74-year-old M	Scalp	T3/T4A	Tumor Diameter (4.0cm) Depth of Invasion (Bone)	Excision ART Adjuvant Chemotherapy	LR DSD	17
<i>Matched Case Treated with SM</i>	73-year-old M	Forehead	T2B/T3	Tumor Diameter (2.3cm) Depth of Invasion (Muscle)	MMS		20
Poor Outcomes from Large Caliber PNI Analysis							
6	80-year-old M Kidney Transplant	Medial Canthus	T2B/T3	Depth of Invasion (Muscle) Large-Caliber PNI	MMS	LR DSD	3
7	58-year-old M Lung Transplant	Scalp	T2B/T3	Tumor Diameter (2.7cm) Depth of Invasion (Galea) Large-Caliber PNI (>3 nerves)	MMS	LR In Transit Metastasis	3
8	92-year-old M	Scalp	T2B/T3	Tumor Diameter (3.8cm) Depth of Invasion (Galea) Large-Caliber PNI	MMS	LR	5

Abbreviations: S+ART, surgery and adjuvant radiation; SM, surgery monotherapy, M, male; MMS, Mohs micrographic surgery; ART, adjuvant radiation; LR, local recurrence; DM, distant metastasis; DSD, disease specific death; PNI, perineural invasion; BWH, Brigham and Women's Hospital; AJCC8, American Joint Committee on Cancer, 8th edition

Table 5. Risk factors for SM+ART cases from the matched-case analysis.

Case #	Diameter (cm)	Differentiation	Depth of Invasion	Perineural Invasion	Other Factors
1	6.2	Poor	Bone	PNI (unknown caliber)	Renal transplant recipient
2	1.7	Poor	Muscle	Possible focus of PNI	Required 3 Mohs stages to clear
3	0.4	Poor	Muscle	Multifocal smaller caliber PNI	Foci of single cell infiltration
4	4.0	Poor	Unknown	None	
5	4.2	Poor	Subcutaneous fat	PNI (unknown caliber)	CLL
6*	4.0	Moderate	Parotid	None	Renal transplant recipient
7	3.4	Poor	Subcutaneous fat/14mm	None	
8*	4.0	Well	Bone	None	
9*	1.5	Poor	Fascia	None	Lung transplant recipient LVI
10	2.4	Moderate	Parotid	PNI (unknown caliber)	Renal transplant recipient LVI
11	2.5	Poor	Muscle	None	
12	0.7	Poor	Dermis	PNI (unknown caliber)	Spindle cell histology Required 3 Mohs stages to clear
13	2.8	Poor	Subcutaneous fat/6mm	None	LVI
14	4.0	Poor	Dermis	PNI (unknown caliber)	
15	3.0	Moderate	Muscle	PNI (unknown caliber)	
16*	1.3	Poor	Dermis	Foci suspicious for PNI	Desmoplastic Single cell infiltrative
17	2.0	Well	Subcutaneous Fat	PNI (0.2mm)	
18	0.9	Well	Muscle	PNI (0.125mm)	
19	0.4	Well	Muscle	PNI (0.2mm)	Renal transplant recipient
20	3.6	Moderate	Galea	PNI (0.14mm)	
21	3.0	Poor	Subcutaneous fat	None	LVI
22	2.5	Moderate	Cartilage/5mm	None	Crohn's disease
23	0.5	Poor	Dermis	None	No epidermal connection
24	3.6	Moderate	Cartilage	None	
25	1.0	Poor	Dermis	None	Systemic lupus erythematosus
26	3.0	Well	Subcutaneous fat	PNI (0.125mm)	
27	1.1	Well	Galea	PNI (0.08mm)	
28	3.0	Moderate	Unknown	None	CLL Close but clear margins
29	4.6	Moderate	Galea	None	
30	4.0	Poor	Bone	PNI (unknown caliber)	CLL
31	0.8	Well	Muscle	PNI (0.2mm)	

Abbreviations: PNI, perineural invasion; LVI, lymphovascular invasion; CLL, chronic lymphocytic leukemia

*Tumors that developed a poor outcome

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Capsule Summary

- Radiation is sometimes used after surgery for cutaneous squamous cell carcinoma.
- Outcomes were the same with or without radiation in a matched analysis and subgroup analysis of cases with nerve invasion. Only 8% of cases recurred. All but 3 were still curable. Studies are needed determining which patients need radiation.