Management of Invasive Squamous Cell Carcinomas of the Conjunctiva

ALEXANDRA SANTONI, JULIETTE THARIAT, CÉLIA MASCHI, JOEL HERAULT, STÉPHANIE BAILLIF, SANDRA LASSALLE, MARIE LAURE PEYRICHON, JULIA SALLERON, AND JEAN-PIERRE CAUJOLLE

• PURPOSE: **Ocular surface squamous neoplasia includes a spectrum of diseases from dysplasia to invasive squamous cell carcinoma (SCC) of the conjunctiva. Whether the degree of invasion influences outcomes is debated. We evaluated the outcomes and management of conjunctival carcinomas defined as ≤0.2 mm invasion of the chorion (microinvasive; miSCC) or over (SCC).**

• DESIGN: **Retrospective case series.**

• METHODS: **Clinical, tumor, and therapeutic characteristics and outcomes were collected for consecutive patients with histology-proven invasive conjunctival miSCC/SCC treated between 2002 and 2017.**

• RESULTS: **Patients were 70% men, ≥70 years old (56%), with carcinomas of the bulbar conjunctiva (83.0%). Limbal, corneal, and/or scleral involvement were present in 70.4%, 42.6%, and 27.8%, respectively. Patient characteristics, tumor characteristics, and no-touch surgery rates were similar between the 39 SCC and 15 miSCC. However, mitomycin was performed in 93.3% and 20.5% of miSCC and SCC, respectively ($P < .001$). Proton therapy was performed in 0% and 92.0% of miSCC and SCC, respectively ($P < .001$). SCC received mitomycin in case of tumoral resection margins, respectively ($P = .018$). The 24-month incidence of local relapse was 14.8%, including 20% and 12% for miSCC and SCC, respectively ($P = .079$). Irradiation was the only prognostic factor associated with a lower risk for local relapse (hazard ratio [0.25]; $P = .045$). There were 2 cancer-related deaths (2%). Mild/moderate anterior segment complications occurred in one third of the patients.**

• CONCLUSIONS: **miSCC had slightly worse relapse rates compared with SCC. Postoperative proton therapy, performed in SCC only, was associated with a lower risk for relapse. (Am J Ophthalmol 2019;200:1–9. © 2018 Elsevier Inc. All rights reserved.)**

Accepted for publication Nov 30, 2018.

From the Departments of Ophthalmology (A.S., C.M., S.B., J.-P.C.) and Biopathology (S.L.), Pasteur 2 Teaching Hospital, Nice, France; Department of Radiation Oncology, Francois Baclesse Cancer ARCHADE Center, Normandie Universite-Unicaen, Caen, France (J.T.); Department of Radiation Oncology, Antoine-Lacassagne Cancer Center, Nice, France (J.H., M.L.P.); and Department of Biostatistics, Institut de Cancérologie de Lorraine, Université de Lorraine, Vandœuvre-lès-Nancy, France (J.S.).

Inquiries to Juliette Thariat, Department of Radiation Oncology, Centre Baclesse/ARCHADE, 4 rue General Harris, Caen, France; e-mail: jthariat@gmail.com

OCULAR SURFACE SQUAMOUS NEOPLASIA (OSSN) is a spectrum of diseases ranging from dysplasia to invasive squamous cell carcinoma (SCC). SCCs is one of the most common malignant tumors of the ocular surface,[1,2] with an incidence that varies geographically from 0.3 to 35 per million inhabitants.[3] A trend toward increasing incidence has been reported, and it may be due to ultraviolet light exposure and human papillomavirus infection.

The mainstay of treatment is the standard "no-touch" surgical technique, which consists of removing the tumor with clear margins without touching the tumor.[4] It may be associated with absolute alcohol corneal epitheliectomy in case of corneal involvement and cryotherapy of the cut conjunctival edge.[4–6] Owing to the high recurrence rates of OSSN, varying from 5% to 53% after surgery,[7] various adjuvant treatments have been used. These include topical ocular treatments and radiotherapy. Adjuvant topical chemotherapy consists of either antimitotic agents, such as mitomycin C (MMC),[8–11] 5-fluorouracil,[12,13] or interferon alpha-2b.[14–16] Topical drugs have limited penetration depth. Adjuvant ocular surface radiotherapy can be performed using proton therapy,[17,18] brachytherapy,[19,20] or electron beam radiation therapy[21] for invasive carcinomas.

SCCs can be both sight- and life-threatening. They can spread into intraocular and orbital structures, and occasionally to regional lymph nodes and distant metastases.[22,23] However, it is debated whether minor invasion may influence the prognosis. Such a distinction is made in routine practice in other tumor types. For example, this distinction between microinvasive and in situ breast adenocarcinomas[24] or between microscopic or macroscopic extracapsular spread in nodes from human papillomavirus squamous cell carcinomas of the head and neck is taken into account to make for therapeutic decision making.[25]

Based on the hypothesis that SCCs and microinvasive SCC (miSCC) might have different prognoses, we conducted a study to evaluate recurrence rates in patients with miSCC and SCC referred to a tertiary care institution.

METHODS

• STUDY POPULATION: This single–tertiary care enter (University Hospital of Nice) Institutional Review Board–approved retrospective case series adhered to the

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.11.024

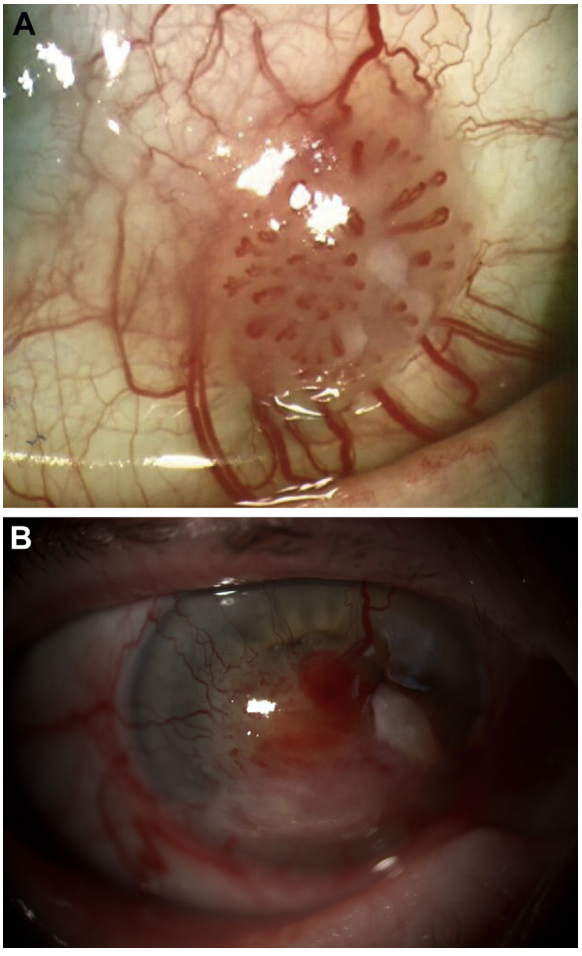

FIGURE 1. Photographs of 2 conjunctival invasive squamous cell carcinomas. (A) Peribulbar conjunctival squamous cell carcinoma with dilated sentinel vessels. (B) Voluminous corneal invasion of invasive squamous cell carcinoma.

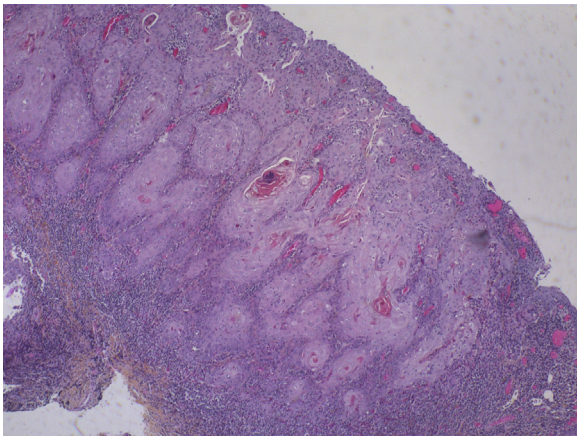

FIGURE 2. Invasive squamous cell carcinoma. Microscopic finding reveals a well-differentiated carcinoma. Conjunctival stroma is infiltrated by nests of neoplastic squamous cells. Basal membrane is largely interrupted. (Hematoxylin-eosin stain.)

tenets of the Declaration of Helsinki. It included review of medical records of consecutive patients with histology-proven miSCC/SCC treated surgically at the Department of Ophthalmology from April 2002 to July 2016.

• **DATA COLLECTION:** Clinical data included age, sex, ethnicity, laterality, symptoms, and previous history of OSSN. Tumor characteristics (Figure 1, Top and Bottom) included conjunctival location (bulbar conjunctiva with or without involvement of the limbus, tarsal conjunctiva, or caruncle); extent into adjacent tissues (corneal and/or scleral involvement, anterior chamber, and/or orbital extension); conjunctival location in quadrants (nasal, temporal, superior, or inferior); tumor size on physical examination, in degrees (less than 90 degrees, between 90 degrees and 180 degrees, or more than 180 degrees of corresponding limbal circumference); and maximum thickness measured by optical coherence tomography or ultrasound biomicroscopy. Tumors were staged based on clinical presentation according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition.[26] Histologic analysis was made by a senior ocular oncology pathologist. Marker silk sutures on excised tissues indicated excised tissue orientation. Several serial cutting lengths of paraffin-embedded tissue were analyzed perpendicular to the major tissue axis in order to analyze the epithelium and substantia propria on the whole excised tissue. Microinvasion (miSCC) was defined as a focal invasion of less than 0.2 mm of the substantia propria while invasion ≥0.2 mm was defined as SCC (Figure 2). Above that depth, the penetration depth of mitomycin can be expected to be more hazardous. Previous history of OSSN lesions before miSCC/SCC were recorded.

Therapeutic modalities, quality of resection, conjunctival reconstruction (conjunctival autograft, amniotic membrane graft, and mucous membrane graft), and complications were recorded. An ocular oncologist performed the no-touch technique, associated with corneal epitheliectomy in case of clinical corneal involvement. Cryotherapy of the excision margins was performed at the discretion of the surgeon. Proton therapy was performed in case of SCC at a total dose of 45 grays (Gy, physical dose) in 8 fractions, but not in miSCC.

Well-circumscribed limbal lesions were treated to 45 Gy in 8 fractions on macroscopic tumor with additional 2.5 mm lateral margins. In case of more diffuse lesions, a 2-step treatment was used, with a large field including the tumor and corresponding ocular quadrants from limbus to conjunctival folds to 31.2 Gy and a reduced boost to the macroscopic tumor with additional 2.5 mm lateral margins for 13.8 additional Gy. Fiducials were used to accurately define tumor extents and corresponding radiation fields. A brass collimator shaped the beam laterally in all cases. The beam was modulated using a range filter and a

modulation wheel so that the deepest part of the tumor volume would be irradiated with 2.5 anteroposterior security margins. An individually shaped compensator was brought into the beam to modify the range of the protons so that the eye was irradiated only at a depth of 2.5 mm behind the tumor margins and ocular surface. Lid retraction (to spare the palpebra from the radiation field) was performed after 2008 whenever clinically possible.

Postoperative mitomycin was used at a concentration of 0.02% or 0.04%, depending on quality of the ocular surface. In SCC undergoing proton therapy, 5 patients out of 15 with positive margins had mitomycin (33%), whereas none of the 16 patients with negative margins had any ($P = .018$) (for 5 patients, mitomycin was not documented and was considered as missing data). When it was associated with proton therapy, mitomycin was started 1 month after irradiation to avoid the cumulative acute toxic irritative effects of both irradiation and mitomycin.

A recurrence was defined as the appearance of a new clinical lesion that was not present on immediately postoperative slit-lamp photography. Salvage treatments of local relapses were reported.

• **STATISTICAL ANALYSIS:** Statistics were performed with the Statistical Analysis System software version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). Qualitative parameters were described as frequency and percentage and quantitative parameters as median and interquartile range. Incidence of local relapse was described by the cumulative incidence function and prognostic factors were investigated by the Fine and Gray model in order to take into account death and metastasis relapse as competing risks. Overall survival was described by Kaplan-Meier method. A P value of less than .05 was considered statistically significant in the multivariate model.

RESULTS

• **PATIENT AND TUMOR CHARACTERISTICS:** Fifty-four patients with a histology-proven diagnosis of miSCC/SCC were included. There were 39 SCCs and 15 miSCCs. Mean age at diagnosis was 68.5 years (median, 71 years; interquartile range, 64-79 years). Among them, 3 patients had a history of noninvasive OSSN and 11 had a history of miSCC/SCC before referral to our center (3 miSCC and 8 SCC).

Patient, tumor, and treatment characteristics are shown in Table 1. Among symptoms, discomfort and itching were the most frequent symptom. Clinical T stage was T1, T2, and T3 in 6 (42.9%), 2 (14.2%), and 6 (42.9%) of miSCC and 9 (23.1%), 7 (17.9%), and 23 (59.0%) of SCC ($P = .369$). There were no T4. All miSCC/SCC were treated surgically using the no-touch technique. Surgical margins after surgery at our hospital were negative in 24 (51.1%) of the patients. Twenty-five (46.3%) patients underwent conjunctival reconstruction. Topical mitomycin was used in 14 (93.3%) of the miSCC and 8 (20.5%) of the SCC ($P < .001$, Table 1). Proton therapy was used in 36 of the 39 SCC (92.3%) but in none of the 15 miSCC ($P < .001$, Table 1). The 3 SCC patients were not treated with proton therapy because of poor general status.

Side effects of treatments were irritative symptoms such as hyperemia, slight eyelid swelling, and superficial punctate keratitis in 20 (37.0%) patients after mitomycin. Radiation-induced complications consisted of cataract in 14 (38.9%), lid alopecia in 11 (30.6%), eyelid dermatitis in 5 (13.9%), neovascular glaucoma in 3 (8.3%), cutaneous retraction in 2 (5.6%), lacrimal duct stenosis in 2 (5.6%), and retinal vein occlusion in 2 (5.6%) of the patients. One patient had basal cell carcinoma of the inner eyelid 5 years after irradiation.

• **OUTCOMES:** There were 4 local relapses in the 15 miSCC patients and 4 local relapses in the 39 SCC patients. Mean follow-up was 24 months (interquartile range, 15-57 months). The incidence of local relapse at 24 months was 14.8% (95% confidence interval [CI], 6.2%-26.1%) in the overall population, with 20% and 12% for miSCCs and SCCs, respectively ($P = .079$). Median time to local relapse was 11 months (interquartile range, 4.5-18 months). The cumulative incidence of local relapse is shown in Figure 3. Of patients undergoing salvage treatment for relapsed miSCC/SCC, 2 had another recurrence. Orbital involvement at relapse was noted in 2 SCC patients.

Regional lymph node metastasis occurred in 4 (7.4%) patients, within a median time of 41.0 months: 2 were located in cervical lymph nodes and 2 in both cervical lymph nodes and the parotid gland. Systemic metastases occurred in 2 (3.7%) cases. Liver and bones were both affected in 1 case, and lungs alone in the other.

At last follow-up, 10 (18.5%) patients had died. Overall survival was 95.7% (95% CI, [83.5%-98.9%]) at 24 months and 83.4% (95% CI, [62.7%-93.2%]) at 60 months. Overall survival is shown in Figure 4. Two (3.7%) deaths were attributable to a metastatic conjunctival carcinoma; they occurred at 21 and 67 months.

• **PROGNOSTIC FACTORS OF LOCAL RELAPSE:** The prognostic factors of local relapse on univariate analysis are listed in Table 2.

On univariate analysis, only proton therapy was a significant protective factor against local relapse (Table 2). Multivariate analysis could not be computed owing to a limited number of events (n = 8 local relapses). Cumulative incidence according to proton therapy is shown in Figure 5.

Of the 3 SCC patients who relapsed after trimodal therapy including proton therapy, the relapse occurred in the full dose area. For the third patient, the relapse site could

TABLE 1. Patient, Tumor, and Treatment Characteristics of Invasive and Microinvasive Squamous Cell Carcinoma

Analyzed Factors	Number of Patients (%)	miSCC (N = 15)	SCC (N = 39)	*P* Value
Age				.684
Less than 70	44.44% (24)	40% (6)	46.15% (18)	
More than 70	55.56% (30)	60% (9)	53.85% (21)	
Sex (n = 109)				.510
Male	69.81% (37)	78.57% (11)	66.67% (26)	
Female	30.19% (16)	21.43% (3)	33.33% (13)	
Medical history				.210
No previous history	37.04% (20)	53.33% (8)	30.77% (12)	
Surgery before referral	37.04% (20)	20% (3)	43.59% (17)	
Treatment before referral at recurrence	25.93% (14)	26.67% (4)	25.64% (10)	
Laterality				.177
Right eye	48.15% (26)	33.33% (5)	53.85% (21)	
Left eye	51.85% (28)	66.67% (10)	46.15% (18)	
Symptoms				.999
Absent	70.37% (38)	73.33% (11)	69.23% (27)	
Present	29.63% (16)	26.67% (4)	30.77% (12)	
Involved areas				.920
Bulbar conjunctiva without limbus	12.96% (7)	13.33% (2)	12.82% (5)	
Bulbar conjunctiva with limbus	70.37% (38)	73.33% (11)	69.23% (27)	
Tarsal conjunctiva or caruncle	16.67% (9)	13.33% (2)	17.95% (7)	
Extent into adjacent tissues				
Corneal involvement				
No	57.41% (31)	60% (9)	56.41% (22)	.811
Yes	42.59% (23)	40% (6)	43.59% (17)	
Scleral involvement				
No	72.22% (39)	80% (12)	69.23% (27)	.515
Yes	27.78% (15)	20% (3)	30.77% (12)	
Tumor circumference				.684
Less than 90 degrees	55.56% (30)	60% (9)	53.85% (21)	
More than 90 degrees	44.44% (24)	40% (6)	46.15% (18)	
Clinical T stage				.369
T1	29.63% (15)	42.86% (6)	23.08% (9)	
T2	16.67% (9)	14.29% (2)	17.95% (7)	
T3	53.70% (29)	42.86% (6)	58.97% (23)	
T4	0 (0)	0% (0)	0 (0)	
Surgical margins (n = 47)				.374
Negative	51.06% (24)	61.54% (8)	47.06% (16)	
Positive	48.94% (23)	38.46% (5)	52.94% (18)	
Adjuvant treatment				.482
No	3.7% (2)	6.67% (1)	2.56% (1)	
Yes	96.3% (52)	93.33% (14)	97.44% (38)	
Surgery				<.001*
Surgery without proton	33.33% (18)	100% (15)	7.69% (3)	
Surgery with proton	66.67% (36)	0% (0)	92.31% (36)	
Surgery				.205
Surgical resection without graft	52.83% (28)	66.67% (10)	47.37% (18)	
Surgical resection with graft	47.17% (25)	33.33% (5)	52.63% (20)	
Surgery and mitomycin				<.001*
Surgical resection without mitomycin	59.26% (32)	6.67% (1)	79.49% (31)	
Surgical resection and mitomycin 0.02%	29.63% (16)	73.33% (11)	12.82% (5)	
Surgical resection and mitomycin 0.04%	11.11% (6)	20% (3)	7.69% (3)	

AJCC = American Joint Committee on Cancer; miSCC= microinvasive squamous cell carcinoma; SCC = invasive squamous cell carcinoma. Asterisk (*) indicates statistically significant *P* value.

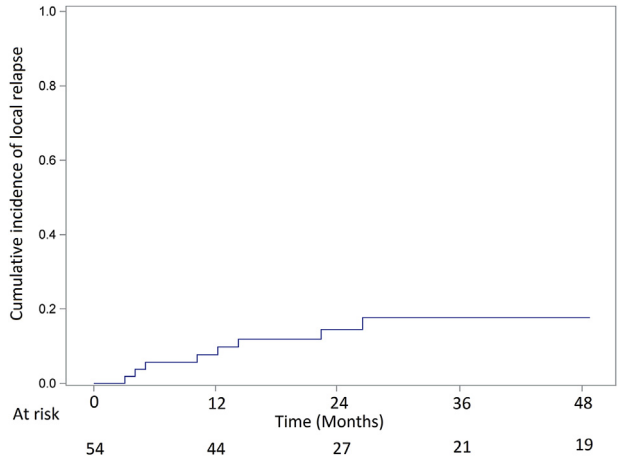

FIGURE 3. Cumulative incidence of local relapse in the treatment of invasive conjunctival carcinoma.

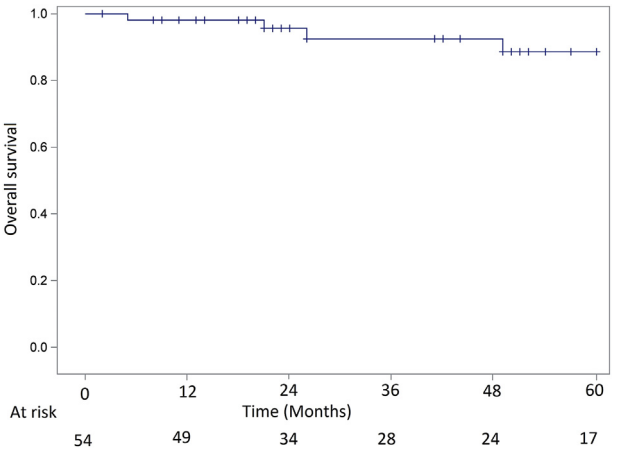

FIGURE 4. Overall survival in the treatment of conjunctival carcinoma.

not be repositioned on the proton field (relapse managed at outside institution).

DISCUSSION

BOTH MISCC AND SCC HAVE A DISRUPTION OF THE basement membrane, which confers a theoretical risk for regional and distant metastases. However, the extent of invasiveness is minimal in miSCC and several institutions have considered it safe to limit adjuvant treatments (and treat miSCC as in situ carcinomas), whereas others have advocated the same aggressive multimodal strategy as for SCCs. This series represents a unique opportunity to compare the characteristics and outcomes between SCCs and miSCCs. A homogenous practice was used for miSCCs, as none of the miSCC patients were advocated for adjuvant ocular surface irradiation. The assumption was that mitomycin was sufficient to treat the 0.2 mm of invasion under the basement membrane. While mitomycin can only have a superficial effect, it was used in this series in SCC cases with incomplete microscopic resection where the surgical cut was in contact with some neoplastic cells (ie, when the no-touch technique failed with a subsequent risk for conjunctival tumor graft). In the other SCC, given the no-touch technique, mitomycin was not used and proton therapy was performed.

The trend for a higher local recurrence rate of miSCCs compared to SCCs is intriguing but has also been reported by others.[6] In the current series, the characteristics of miSCC and SCC only differed with respect to 2 therapeutic options, that is, irradiation by proton therapy and mitomycin: The former was only performed in SCC while the latter was performed in all but 1 miSCC and only 2 SCC patients. Prognostic factors on univariate analysis were proton therapy only, which was associated with a lower risk for local relapse. Mitomycin was not associated with a lower risk for local relapse. In contrast to several other studies,[7,23,27] the recurrence rates were rather low (below 20%) in SCCs using a trimodal therapeutic strategy (surgery, proton therapy, mitomycin). Clinical primary (T) stage was not associated with poorer local relapse rates in this series.

Intriguingly, miSCC had slightly higher crude local relapse rates despite being acknowledged as being less aggressive than SCC histologically. As it is the histology itself that made physicians advocate less intensive treatment, histology and treatment cannot be assessed as independent prognostic factors. Surgery and quality of resection, a major endpoint in other series, were similar in miSCC and SCC. The only difference-favorable prognostic factor in terms of local relapse was adjuvant irradiation by proton therapy, which was delivered in SCCs only. Whether proton therapy could have improved recurrence rates in miSCCs cannot be ascertained in this study (owing to dependence between histology and treatment). However, the treatment of miSCC was less intensive only with respect to proton therapy, as mitomycin was quite systematically performed in miSCC, which was not the case in SCC. Thus, the observation of a lower relapse rate with irradiation by proton therapy may be considered hypothesis-generating. As relapse rates in SCC (despite 59% T3) were slightly better than in miSCC, this observation may also suggest that proton therapy was an important prognostic factor and could have benefited miSCC also. However, this is a retrospective study. Other differences may not have been accounted for here and the overlap between histology and therapy should engender caution in the interpretation of these results. Although there are few publications on that topic, it should be noted that several teams advocate proton therapy systematically for miSCC in routine practice. Altogether, this change in strategy cannot be taken lightly owing to side effects of ocular surface irradiation. To be practice-changing only

TABLE 2. Univariate Analysis of Local Relapse

Analyzed Factors	Number of Patients (%)	Number of Events	Cumulative Incidence et 2 Years	HR and 95% CI	*P* Value
Age					
Less than 70	44.44% (24)	2	9%	1	
More than 70	55.56% (30)	6	19%	2.48 [0.5;12.2]	.265
Sex (n = 109)					
Male	69.81% (37)	6	14%	1	
Female	30.19% (16)	2	16%	0.75 [0.16;3.49]	.71
Medical history					
No previous history	37.04% (20)	5	29%	1	
Surgery before referral	37.04% (20)	1	0%	0.15 [0.02;1.09]	.061
Previous treatment before referral for relapse	25.93% (14)	2	17%	0.59 [0.11;3.02]	.522
Surgery					
Outside tertiary care center	42.59% (23)	2	10%	1	
At tertiary care center	57.41% (31)	6	18%	2.13 [0.44;10.34]	.351
Laterality					
Right eye	48.15% (26)	2	5%	1	
Left eye	51.85% (28)	6	23%	3.38 [0.78;14.56]	.102
Physical signs or symptoms at diagnosis					
Absent	70.37% (38)	4	8%	1	
Present	29.63% (16)	4	29%	2.58 [0.68;9.87]	.165
Initial location					
Bulbar conjunctiva without limbus	12.96% (7)	1	14%	1	
Bulbar conjunctiva with limbus	70.37% (38)	5	12%	0.70 [0.08;5.94]	.744
Tarsal conjunctiva or caruncle	16.67% (9)	2	24%	1.34 [0.11;16.24]	.819
Spread into adjacent tissues					
Corneal involvement					
No	57.41% (31)	4	13%	1	
Yes	42.59% (23)	4	17%	1.38 [0.35;5.41]	.649
Scleral involvement					
No	72.22% (39)	5	12%	1	
Yes	27.78% (15)	3	21%	1.42 [0.33;6.15]	.638
Tumor circumference					
Less than 90 degrees	55.56% (30)	3	11%	1	
More than 90 degrees	44.44% (24)	5	20%	2.32 [0.55;9.74]	.252
Squamous cell carcinoma					
Microinvasive (miSCC)	27.78% (15)	4	12%	1	
Invasive (SCC)	72.22% (39)	4	20%	3.34 [0.87;12.85]	.079
T stage					
T1	23.08% (9)	2	13%	1	-
T2	17.95% (7)	1	11%	0.93 [0.08;11.25]	.953
T3	58.97% (23)	5	17%	1.29 [0.25;6.76]	.758
Surgical margins (n = 47)					
Negative	51.06% (24)	2	10%	1	
Positive	48.94% (23)	6	23%	3.42 [0.72;16.29]	.123
Surgery					
Surgical resection without protons	33.33% (18)	1	23%	1	
Surgical resection with protons	66.67% (36)	7	10%	0.25 [0.06;0.97]	.045*
Surgery					
Surgical resection without graft	52.83% (28)	4	15%	1	
Surgical resection with graft	47.17% (25)	4	14%	1.1 [0.29;4.17]	.894
Surgery and mitomycin					
Surgical resection without mitomycin	59.26% (32)	3	11%	1	-
Surgical resection and mitomycin	41.74% (22)	5	19%	2.72 [0.68;10.88]	.158

Asterisk (*) indicates statistically significant *P* value.

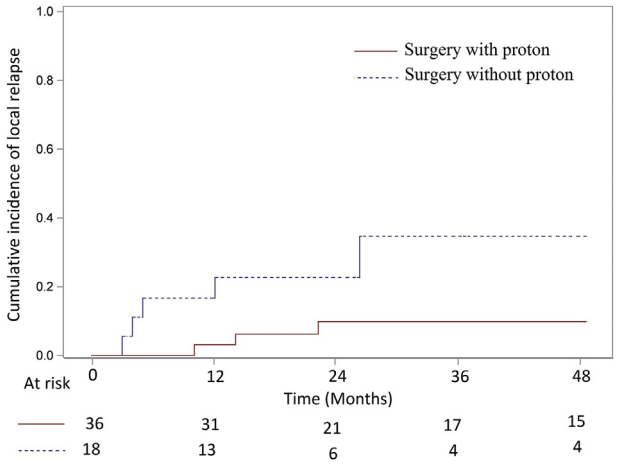

FIGURE 5. Incidence of local relapse according to proton therapy (dashed red line represents squamous cell carcinomas and solid blue line minimally invasive squamous cell carcinomas).

on this series, one should have confirmatory series from prospective multicentric studies using a methodology to account for attrition biases or, ideally, a randomized study would be necessary.

Series of ocular surface neoplasia (not restricted to miSCC/SCC but also including dysplasia) report an average time to recurrence of 24 months.[7,27] The present series was in accordance with published data with respect to average time to relapse and has a median time to relapse of 11 months after oncologic treatment at our institution. Local relapses may be more aggressive and further lead to regional metastases (mostly in the parotid/facial and cervical nodal areas) and distant metastases in our series. They were a cause of death in 2 out of the 8 patients who relapsed. Thus, optimal local treatment is critical.

The other risk factors of recurrence included clear resection margins, which is in accordance with the literature.[7,23,28] The relatively low rate of local relapse in our series may be due to exclusion of dysplasia and to the systematic no-touch surgery. As SCCs may not be so easy to diagnose in routine practice, prior management before referral of atypical conjunctival lesions may be best avoided or should follow the no-touch surgery rule. In case this technique is not feasible, patients should be referred to ocular oncology centers firsthand if possible.[23]

In the 3 patients who relapsed after irradiation by proton therapy, 2 at least relapsed in field, suggesting tumor radioresistance. Whether the dose should have been higher cannot be investigated. Of note, the dose delivered for conjunctival carcinomas is the same as that for conjunctival melanomas, although melanomas are more radioresistant than carcinomas in general. The advantage of proton therapy in comparison to electron therapy is that the dose distribution can be better conformed laterally, that is, sparing more ocular tissues by avoiding the mushroom shape obtained with electrons.

A third of the patients had complications related with surgery and mitomycin, such as irritative symptoms. Radiation-induced complications owing to irradiation of the anterior segment also occurred in a third of the patients but may persist in the long term, in contrast to those attributable to mitomycin. Irradiation of the goblet cells of the conjunctiva can be associated with dry eye syndrome, but this was not a major issue in this series. Field reduction after 31.2 Gy was performed in all cases (or from the start in purely limbal lesions). Because most goblet cells are located in the conjunctival folds, field reduction probably helped to limit occurrence of a dry eye syndrome. In contrast, lid alopecia was observed in about a third of the patients. Lid retraction may not be not feasible in case radiation fields need to include the conjunctival folds while palpebral elasticity is insufficient. The proton beam usually included part of the iris and, in non–purely limbal cases, the ciliary body. Rubeosis iridis was not reported in our series. The dose delivered to the iris and ciliary body was lower and more fractionated than what is performed in uveal melanomas (45 Gy in 8 fractions, vs 52 Gy in 4 fractions), which might explain why dilated iris vessels or true rubeosis are more frequent in uveal melanomas treated with proton beams. Secondary glaucoma occurred in 3 patients. Radiation-induced inflammation may occur following irradiation of these structures and secondary production of vascular endothelial growth factor, which might induce secondary glaucoma.

In most institutions, proton beam is not available, and brachytherapy is a very good complementary method of treating invasive conjunctival SCC. The shape of brachytherapy plaques has to be personalized to the shape of the tumor. Tumors that exhibit limited spread in the mucosal part of the eyelids or include the caruncle may, however, be more easily treated with proton therapy. With proton therapy, depth distribution can be modulated using a compensator so that dose is limited behind the eye surface to spare normal tissues. To that extent and given the observed side effects in this series, proton therapy and brachytherapy may be worth being compared to assess the risk/benefit ratio of both techniques in conjunctival tumors.

Similar to retrospective studies or early-phase trials, this selected population of patients might not be representative of a typical miSCC/SCC population. Another limitation is that this retrospective study suffered from some missing data, such as surgical margin involvement (8% of missing data). However, conjunctival tissues are fragile and difficult to process for histopathologic evaluation. Thus, biopsy and operative specimens are often quite small and difficult to analyze. Biopsies and operative specimens may be best analyzed in expert ocular oncology tertiary care centers.

To conclude, this study revealed slightly higher relapse rates in miSCCs compared to SCCs. Adjuvant proton therapy might be beneficial regardless of the degree of invasion. Whether this may be attributed to adjuvant irradiation using proton therapy or to histology itself remains to be confirmed with larger multicenter and prospective cohort studies.

FUNDING/SUPPORT: NO FUNDING OR GRANT SUPPORT. FINANCIAL DISCLOSURES: THE FOLLOWING AUTHORS HAVE NO financial disclosures: Alexandra Santoni, Juliette Thariat, Célia Maschi, Joel Herault, Stéphanie Baillif, Sandra Lassalle, Marie Laure Peyrichon, Julia Salleron, and Jean-Pierre Caujolle. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Nanji AA, Mercado C, Galor A, Dubovy S, Karp CL. Updates in ocular surface tumor diagnostics. *Int Ophthalmol Clin* 2017;57(3):47–62.
2. Shields CL, Demirci H, Karatza E, Shields JA. Clinical survey of 1643 melanocytic and nonmelanocytic conjunctival tumors. *Ophthalmology* 2004;111(9):1747–1754.
3. Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, Shields JA. Conjunctival tumors: review of clinical features, risks, biomarkers, and outcomes–the 2017 J. Donald M. Gass Lecture. *Asia Pac J Ophthalmol (Phila)* 2017;6(2):109–120.
4. Shields JA, Shields CL, De Potter P. Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture. *Arch Ophthalmol* 1997;115(6):808–815.
5. Peksayar G, Soyturk MK, Demiryont M. Long-term results of cryotherapy on malignant epithelial tumors of the conjunctiva. *Am J Ophthalmol* 1989;107(4):337–340.
6. Blasi MA, Maceroni M, Sammarco MG, Pagliara MM. Mitomycin C or interferon as adjuvant therapy to surgery for ocular surface squamous neoplasia: comparative study. *Eur J Ophthalmol* 2018;28(2):204–209.
7. Galor A, Karp CL, Oellers P, et al. Predictors of ocular surface squamous neoplasia recurrence after excisional surgery. *Ophthalmology* 2012;119(10):1974–1981.
8. Birkholz ES, Goins KM, Sutphin JE, Kitzmann AS, Wagoner MD. Treatment of ocular surface squamous cell intraepithelial neoplasia with and without mitomycin C. *Cornea* 2011;30(1):37–41.
9. Hirst LW. Randomized controlled trial of topical mitomycin C for ocular surface squamous neoplasia: early resolution. *Ophthalmology* 2007;114(5):976–982.
10. Viani GA, Fendi LI. Adjuvant treatment or primary topical monotherapy for ocular surface squamous neoplasia: a systematic review. *Arq Bras Oftalmol* 2017;80(2):131–136.
11. Lee JH, Kim YH, Kim MS, Kim EC. The effect of surgical wide excision and amniotic membrane transplantation with adjuvant topical mitomycin C treatment in recurrent conjunctival–corneal intraepithelial neoplasia. *Semin Ophthalmol* 2014;29(4):192–195.
12. Al-Barrag A, Al-Shaer M, Al-Matary N, Al-Hamdani M. 5-Fluorouracil for the treatment of intraepithelial neoplasia and squamous cell carcinoma of the conjunctiva, and cornea. *Clin Ophthalmol* 2010;4:801–808.
13. Parrozzani R, Frizziero L, Trainiti S, et al. Topical 1% 5-fluoruracil as a sole treatment of corneoconjunctival ocular surface squamous neoplasia: long-term study. *Br J Ophthalmol* 2017;101(8):1094–1099.
14. Kim HJ, Shields CL, Shah SU, Kaliki S, Lally SE. Giant ocular surface squamous neoplasia managed with interferon alpha-2b as immunotherapy or immunoreduction. *Ophthalmology* 2012;119(5):938–944.
15. Shah SU, Kaliki S, Kim HJ, Lally SE, Shields JA, Shields CL. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: outcomes based on American Joint Committee on Cancer classification. *Arch Ophthalmol* 2012;130(2):159–164.
16. Shields CL, Kaliki S, Kim HJ, et al. Interferon for ocular surface squamous neoplasia in 81 cases: outcomes based on the American Joint Committee on Cancer classification. *Cornea* 2013;32(3):248–256.
17. Caujolle JP, Maschi C, Chauvel P, Herault J, Gastaud P. [Surgery and additional protontherapy for treatment of invasive and recurrent squamous cell carcinomas: technique and preliminary results]. *J Fr Ophtalmol* 2009;32(10):707–714.
18. El-Assal KS, Salvi SM, Rundle PA, Mudhar HS, Rennie IG. Treatment of invasive ocular surface squamous neoplasia with proton beam therapy. *Eye (Lond)* 2013;27(10):1223–1224.
19. Arepalli S, Kaliki S, Shields CL, Emrich J, Komarnicky L, Shields JA. Plaque radiotherapy in the management of scleral-invasive conjunctival squamous cell carcinoma: an analysis of 15 eyes. *JAMA Ophthalmol* 2014;132(6):691–696.
20. Laskar S, Gurram L, Laskar SG, Chaudhari S, Khanna N, Upreti R. Superficial ocular malignancies treated with strontium-90 brachytherapy: long term outcomes. *J Contemp Brachytherapy* 2015;7(5):369–373.
21. Graue GF, Tena LB, Finger PT. Electron beam radiation for conjunctival squamous carcinoma. *Ophthalmic Plast Reconstr Surg* 2011;27(4):277–281.
22. Cervantes G, Rodriguez AA Jr, Leal AG. Squamous cell carcinoma of the conjunctiva: clinicopathological features in 287 cases. *Can J Ophthalmol* 2002;37(1):14–19. discussion 19-20.
23. Yousef YA, Finger PT. Squamous carcinoma and dysplasia of the conjunctiva and cornea: an analysis of 101 cases. *Ophthalmology* 2012;119(2):233–240.
24. Rabinovitch RA, Solin LJ, Shank BM, et al. Ductal carcinoma in situ and microinvasive disease. American College of Radiology. ACR Appropriateness Criteria. *Radiology* 2000;215(Suppl):1137–1152.
25. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers-major changes in the American Joint Committee

on Cancer eighth edition cancer staging manual. CA *Cancer J Clin* 2017;67(2):122–137.
26. Conway RM, Graue GF, Pelayes DE, et al. Conjunctival Carcinoma. American Joint Committee on Cancer (AJCC). AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
27. Miller CV, Wolf A, Klingenstein A, et al. Clinical outcome of advanced squamous cell carcinoma of the conjunctiva. *Eye (Lond)* 2014;28(8):962–967.
28. Yin VT, Merritt HA, Sniegowski M, Esmaeli B. Eyelid and ocular surface carcinoma: diagnosis and management. *Clin Dermatol* 2015;33(2):159–169.