Supplementary materials:

Table S1: Studies using topical and intralesional therapy for perioral cutaneous cancer (including actinic cheilitis, lip squamous cell carcinoma and perioral lentigo maligna).

Topical therapy in perioral cutaneous cancer									
Topical therapy for actinic cheilitis									
Therapeutic modality	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up (months)**	**Recurrence**	**Comments**
IMI	Husein-El Ahmed et al, 2019[1,5,9,10]	Clinical trial	10	IMI 5% thrice a week for 4 weeks	CR: 50% PR: 40% NR: 10%	N/A	8.7	0	Patient satisfaction index: 5.4/10.
	Smith et al, 2002[5,6,9]	Retrospective study	15	IMI 5% thrice a week for up to 6 weeks	CR: 100% (at 4 weeks after end)	N/A	7.3	0	Additional treatment duration may not be more effective
	McDonald et al, 2010[6,10]	Retrospective study	5	IMI 5% 5 times a week for up to 6 weeks	CR: 100%	CR: 100%	1	-	-
	Spyridonos et al, 2014[6]	Prospective study	8	IMI 5% once daily for 5 weeks	CR: 62,5% PR: 37,5%	N/A	6	-	-
5-FU	Epstein, 1977[5,9]	Prospective study	12	5-FU 5% 3-4 times a day	CR: 100%	N/A	22	16.7%	-

				for a mean of 12 days					
	Robinson et al, 1989[5,9]	Prospective study	10	5-FU 5% thrice a day for 4 weeks	N/A	N/A	50	50%	Recurrences proven by biopsy
	Warnock et al, 1981[9]	Prospective study	6	5-FU 1% Twice a day for 2-3 weeks	CR: 100%	PR: 83% NR: 16%	1-2	-	Biopsy taken after post-treatment inflammation subsided
PDT	Bakirtzi et al, 2021[9]	Systematic review (13 studies)	241	Daylight, ALA or MAL-PDT over 1-6 sessions	CR: 66.7%	CR: 49.5%	14.8	14.1%	Discontinuation rate: 5.9%
	Lai et al, 2020[10]	Systematic review (18 studies)	257	Daylight, ALA or MAL-PDT over 1-6 sessions	CR: 68.9% PR: 27.6& NR: 8.3%	CR: 42.5%	11.1	12.6%	Discontinuation rate: 6.2%
Daylight PDT	Fai et al, 2015[9]	Prospective study	10	2 sessions of daylight MAL-PDT 1-2 weeks apart	CR: 70%	N/A	7	28.6%	-
	Lai et al, 2020[10]	Systematic review (3 studies)	23	Daylight MAL-PDT over a mean	CR: 82.6% PR: 9.1%	CR: 100%	20.5	13%	-

				of 2.5 sessions					
	Andreadis et al, 2020[13]	Prospective study	22	2 sessions of daylight MAL-PDT a week apart	CR: 81.8% PR: 9.1%	N/A	12	11.1%	Painless in 80% of cases. 2 patients lost to follow-up
	Levi et al, 2019 [9,14]	Prospective study	11	Daylight MAL-PDT over a mean of 2 sessions	CR: 91%	CR: 100% (45% biopsied)	30	10%	-
Laser-mediated PDT	Bakirtzi et al, 2021[9]; Lai et al, 2020[10]	Systematic reviews (2 studies)	33	ALA-dye 595 and MAL-Er:YAG up to 3 sessions	CR: 75.8% PR: 10.5%	N/A	7.5	6.1%	-
PDT + imiquimod 5%	Sotiriou et al, 2011 [10,16]	Prospective study	34	2 MAL-PDT 2 weeks apart followed by IMI 5% thrice a week for 4 weeks	CR: 90% PR: 10%	CR: 73% (after 12 months)	12	11.1%	4 patients lost to follow-up
IM	Husein-El Ahmed et al, 2019 [1,5,9]	Clinical trial	10	IM 0.015% on 3 consecutive days	CR: 40% PR: 30% NR: 30%	N/A	6	0	Non-inferior to IMI 5% and shorter posology
	Flórez et al, 2017 [5,9,17]	Case series	7	IM 0.015% on 3 consecutive days	CR: 42.9% PR: 57.1%	N/A	2	-	Partial responses represented an improvement

									over 75% from basal.
	Rossini et al, 2021 [5,18]	Prospective study	14	IM 0.015% on 3 consecutive days	CR: 0% PR: 100%	CR: 0%	2	-	While objective clinical or histological complete response was not achieved, subjective improvement was noted in all patients.
	Lai et al, 2020[10]	Systematic review (5 studies)	25	IM 0.015% on 3 consecutive days	CR: 52% PR: 38.1% NR: 30%	N/A	5.2	25%	-
Diclofenac	Husein-El Ahmed et al, 2019 [1,5,9]	Clinical trial	10	Diclofenac 3% twice daily for 6 weeks	CR: 20% PR: 40% NR: 40%	N/A	6	0	-
	Lima et al, 2010[5,9]	Prospective study	27	Diclofenac 3% twice daily for 1 to 6 months	CR: 44% PR: 56%	CR: 0% (15 patients)	4.7	-	Those who were biopsied were those with clinical partial response
	Gonzaga et al, 2018[5,9]	Prospective study	31	Diclofenac 3% thrice	CR: 66.7% PR: 20%	N/A	6	0	12 lost to follow up.

				daily for 3 months					5 interrupted treatment due to adverse effects. 2 prolonged 30 additional days
	Bakirtzi et al, 2021[9]	Systematic review (4 studies)	62	Diclofenac 3% twice daily for 1 to 6 months	CR: 45.2%	N/A	4.4	6.5%	-
Topical and intralesional therapy in invasive squamous cell carcinoma of the lip									
Therapeutic modality	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up**	**Recurrence**	**Comments**
Laser-PDT	Yan et al, 2020[19]	Case report	2	Superficial curettage followed by 3 and 8 sessions of ALA-PDT every 2 weeks with a 635 nm laser	CR: 100%	N/A	12 and 24 months	No	-
	Wang et al, 2022[20]	Case report	1	Single-dose Intravenous Hiporfin at doses of 5	Yes	Yes	53 days	No	600 ul of 2 mg/ml hipofin solution injected intralesionally 3

				mg/kg followed by two irradiations (at 48 and 72 h) with 630 nm laser.					hours before each irradiation
	Liang et al, 2020[21]	Case report	1	4 sessions of CO^2 laser + ALA-PDT every week	Yes	N/A	3 years	No	-
PDT	Fargnoli et al, 2015[22]	Case report	1	2 sessions of MAL-PDT	Yes	Yes	2 years	No	-
IMI	Pentangelo et al, 2021[4]	Case report	1	IMI 5% daily for 2 weeks and then once a week.	Yes	N/A	2 years	No	-
IL-MTX	Salido-Vallejo et al, 2016[24]	Retrospective cohort	43 (5 in lower lip)	A single dose of intralesional MTX (syringes of 25 mg/ml) previous to surgery	No	N/A	N/A	N/A	Mean volume reduction of 0.52 cm^2 before surgery. IL-MTX shown to avoid complex surgeries in lip SCC.

	Bergón-Sendín et al, 2019[25]	Prospective study	10	2 doses of 20 mg of IL-MTX	CR: 30% PR: 70%	N/A	N/A	N/A	Mean reduction of 57.3% of major diameter and 68.2% of minor diameter
Intraarterial chemotherapy	Wu et al, 2014[26]	Retrospective study	21	Initial intraarterial daily 50 mg of MTX (mean 8 days) followed by weekly 25 mg of MTX (mean 10 weeks)	CR: 62% PR: 33% NR: 5%	57.1%	69 months	38.4%	12 of 13 patients with clinical CR showed no histological evidence of tumour. Minimal systemic effects
	Yokota et al, 2017[27]	Case report	1	Intraarterial weekly 100 mg/m2 of cisplatin for 5 weeks	Yes	Yes	5 years	No	Minimal systemic effects
Topical and intralesional therapy in perioral lentigo maligna									
Therapeutic modality	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up**	**Recurrence**	**Comments**
Intralesional interferon	Cornejo et al, 2000[66]	Case series	1 (perioral location)	3 million UI of	Yes	N/A	25 months	No	-

				intralesional interferon-alpha thrice weekly up to 29 doses					

ALA: aminolevulinic acid. **CR**: complete response. **IL-MTX**: intralesional methotrexate. **IM**: ingenol mebutate. **IMI**: imiquimod. **MAL**: methyl-aminolevulinic acid. **NR**: non-response. **PDT**: photodynamic therapy. **PR**: partial response. **5-FU**: 5-fluorouracil.

Table S2: Studies using topical and intralesional therapy for periocular cutaneous cancer (including basal cell carcinoma, actinic keratosis squamous cell carcinoma and lentigo maligna).

Topical and intralesional therapy in periocular cutaneous cancer									
Topical and intralesional therapy for periocular basal cell carcinoma									
Therapeutic modaity	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up**	**Recurrence**	**Comments**
IMI	De Macedo et al, 2015[30]	Prospective study	24	IMI 5% 5 times a week for 8-16 weeks.	CR: 89.5%	CR: 89.5%	39.5 months	5.9%	Nodular subtype. 5 patients interrupted treatment. Histological response of 100% after 3 years for lesions smaller than 1 cm.
	Prokosch et al, 2011[31]	Prospective study	5	IMI 5% 5 times a week for 6 weeks	CR: 100%	N/A	7 years	0%	Nodular subtype. 1 patient interrupted treatment.

	García-Martín et al, 2011[32]	Clinical study	15	IMI 5% 5 times a week for 6 weeks	CR: 100%	CR: 100%	24 months	0%	Nodular subtype. Worse tolerated than radiotherapy but better functional results.
	Carneiro et al, 2010[33]	Case series	8 (10 lesions)	IMI 5% 5 times a week for 8-16 weeks	CR: 80%	CR: 80%	11.8 months	0%	Nodular subtype
	Leppäla et al, 2007[34]	Case series	4	IMI 5% 5 times a week for 6 weeks	CR: 100%	CR: 100%	26 weeks	0%	Nodular subtype
	Blasi et al, 2005[35]	Case series	2	IMI 5% 3 times a week for 12 and 8 weeks, respectively	CR: 100%	N/A	1 year	No	Nodular subtype
	Choontanom et al, 2006[36]	Case series	5	IMI 5% 5 times a week for 6 weeks	CR: 80%	N/A	3 years	0%	Nodular subtype. Mean diameter: 10 mm
	Ross et al, 2010[37]	Case series	2	IMI 5% 5 times a week for 6 weeks	CR: 100%	N/A	12 and 9 months	No	-
5-FU	Singh et al, 2021[40]	Retrospective study	14	5-FU 1% Twice daily for up to 6	CR: 57.1% PR: 28.5% NR: 14%	N/A	12 months	N/A	53.3% Nodular, 36.7%

				months until response	(after 12 months)				superficial, 10% basosquamous.
PDT	Cerman et al, 2015[28]	Systematic review	75	Variable number of sessions (typically 2-3; range 1-12)	CR: 77%	N/A	23 months	29.3%	MAL had better CR rates than ALA (87% vs 42%)
Laser-PDT	Li et al, 2019[44]	Case series	8	PDT using 635 nm laser and 5-ALA 10% as a photosensitizer	CR: 100%	CR: 100%	2.8 years	0%	At least an infiltrative BCC is mentioned
Local interferon	Leis-Dosil et al, 2014[46]	Case report	1	Interferon alpha ophthalmic 4 droplets a day (1 million UI per droplet) for 4 months	Yes	N/A	3 years	No	-
	Fenton et al, 2002[47]	Retrospective study	11	Intralesional interferon alpha, 3 million units thrice a week for 2 weeks (total: 18 million)	CR: 100%	CR: 100% (8 patients)	12 months	No	Out of 11 tumours, 10 had been previously treated with surgery with affected margins, and 7 belonged to high-risk histological subtypes.

Local chemotherapy	Meyer et al, 2015[48]	Retrospective study	3	Intralesional bleomycin 1 UI/ml together with lignocaine 2% in a ratio of 4:1, 4 to 8 cycles in 6 to 12 months	CR: 100%	N/A	4 years	No	-
	Kis et al, 2019[49]	Case series	12	1 to 5 electroporation sessions using 250-1000 UI/cm^2 of intralesional bleomycin (3 patients) or 15000 UI/m^2 (9 patients)	CR: 100%	CR: 100% (11 patients)	25.3 months	0%	3 cases of ectropion due to post-procedure scar needed surgical correction.
Topical and intralesional therapy for periocular squamous cell neoplasias									
Therapeutic modality	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up**	**Recurrence**	**Comments**
5-FU	Couch et al, 2012[51]	Retrospective study	14 patients (13 AKs and 1 Bowen)	5-FU 5% Twice daily for 2 weeks, one initial cycle and repetition if partial response, recurrence	CR: 71,4%% PR: 28,5%	N/A	36.6 months	30%	-

	Sharkawi et al, 2011[52]	Case report	1 (Bowen)	5-FU 5% twice daily for 6 weeks	Yes	N/A	3 years	No	-
IMI	Cannon et al, 2011[53]	Retrospective study	47 patients (37 AK, 7 Bowen, 3 BCC)	IMI 5% thrice a week for 4-6 weeks	CR: 72.3%	N/A	16 weeks	0%	9 patients needed interruption of treatment, starting again in 6. One patient lost to follow-up. Complete resolution of adverse effects
	Toso et al, 2022[54]	Case report	1	IMI 3.75% daily over two cycles of 2 course of 2 weeks each (total: 8 weeks)	Yes (complete)	N/A	6 months	No	-
PDT	Rossi et al, 2004[56]	Case report	1 SCC	A single session of 20% ALA-PDT irradiated with an incoherent light source	Yes (complete)	N/A	6 months	No	-
	Calista et al, 2008[58]	Case report	1 in situ SCC (Bowen)	Two sessions of 16% ALA-PDT after curettage, irradiated with	Yes (complete)	Yes (complete)	30 months	No	-

				diode lamp, one week apart					
Laser-PDT	Sunohara et al, 2012[57]	Case report	1 Bowen	Two sessions of ALA-PDT irradiated with pulsed dye laser	Yes (complete)	Yes (complete)	1 month	No	-
PDT + imiquimod 5%	Toledo-Arberola et al, 2012[55]	Case report	1 AK	2 red-light PDT sessions 2 weeks apart with 16% ALA followed by IMI 5% thrice a week for 4 weeks	Yes (complete)	Yes (complete)	N/A	N/A	Immediate response is described after finishing treatment
Diclofenac	Batra et al, 2012[59]	Case series	4 AK	Diclofenac 3% gel twice daily for 1 to 4 months	CR: 100%	N/A	8.3 months	50%	-
Other intralesional treatments	Carriere et al, 2020[60]	Case report	1 SCC	13 cycles of IL-MTX (first 3 cycles of 25 mg, followed by 10 cycles of 50 mg), administered every 2 weeks	Yes (partial)	N/A	6 months	N/A	Sustained tumoral volume reduction of 69%
	Calista et al, 2002[61]	Case report	1 SCC	A single dose of 7.5 mg of intralesional cidofovir	Yes (complete)	Yes (complete at 12 months)	24 months	No	-

	Requena et al, 1990[62]	Case report	1 SCC	4 weekly cycles of 50 mg of intralesional 5-FU, in addition to topical 5-FU 5% once or twice daily and radiotherapy	No	No	N/A	N/A	After therapeutic failure, the patient required extensive surgery, with exenteration and no recurrence after 24 months
Topical and intralesional therapy for periocular lentigo maligna									
Therapeutic modality	**References**	**Type of study**	**Nº of patients**	**Initial regimen**	**Clinical clearance**	**Histological clearance**	**Mean follow-up**	**Recurrence**	**Comments**
IMI	Neumann et al, 2023[38]	Systematic review	21	Variable regimens of IMI 5% ranging from thrice weekly to once daily during 1 to 24 months; alone (13) or combined with other modalities (6 surgery and/or cryotherapy, 2 topical	CR: 85.7% PR: 14.2%	CR: 92% (12 patients)	21.9 months	No	-

				chemotherapy for conjunctival involvement)					
	Misiak-Galazka et al, 2022[65]	Case report	1	2 cycles of IMI 5% 5 times a week during 5 weeks, 2 months apart	Yes (complete)	N/A	2 years	No	First cycle interrupted due to intense inflammation, the same duration was implemented in the second cycle
Local interferon	Cornejo et al, 2000[66]	Case series	1 (periocular location)	6 million UI of interferon-alpha intralesionally thrice weekly for 5 weeks (15 doses)	Yes (complete)	N/A	19 months	No	-
	Carucci et al, 2000[67]	Case report	1 (involving upper and lower eyelid)	3 million UI of interferon-alpha intralesionally in each eyelid, thrice weekly, for a total of 39 million UI in each site.	Yes (complete)	Yes (complete)	N/A	No	Previously treated with excisional surgery. Follow-up time not specified.

AK: actinic keratosis. **ALA**: aminolevulinic acid. **BCC**: basal cell carcinoma. **CR**: complete response. **IL-MTX**: intralesional methotrexate. **IMI**: imiquimod. **MAL**: methyl-aminolevulinic acid. **NR**: non-response. **PDT**: photodynamic therapy. **PR**: partial response. **SCC**: squamous cell carcinoma. **5-FU**: 5-fluorouracil.