Web appendix 4: Supplementary Data on Treatments with less robust data

Laser therapy

One retrospective study examined the treatment of 86 facial SCCs (excluding eyelid carcinomas) with neodymium laser irradiation at a total dose ranging from 118 to 3520 J [1]. Patients were followed for a mean follow-up period of 8.2 years (range 5-11 years). Of a total of 3275 patients (all NMSCs) treated by neodymium laser during the study inclusion period, 438 (14%) were not followed up during the first 5 years. Overall, there were four recurrences in the remaining 86 SCC patients (4.6%). Of the 48 tumours smaller than 1cm in diameter, one recurred (2.1%, 95% CI 0.05 to 11.1), compared with 6.4% of the 31 tumours between 1 and 2 centimetres (95% CI 0.8 to 21.4), and 14.2% (95% CI 0.4 to 57.9) for the seven SCCs greater than 2cm in diameter, but with wide and overlapping confidence intervals these differences were not statistically significant.

Death from disease was not reported in this study.

One year post treatment, 65% of treated areas were clinician assessed as having 'good' cosmetic appearance (lesion not visible) and 35% as 'acceptable' (slightly visible scarring, redness or depigmentation). By year 3, 74% of areas were graded as having good appearance, and the remainder were acceptable.

Most of the observed effects in this study occurred in the first few days post-irradiation, most commonly reactive hyperaemia, oedema and slight soreness which were mild in severity and transient. No systemic adverse events were noted.

Topical Imiquimod

We found nine papers reporting the use of topical Imiquimod to treat SCCs eligible for this review. There was one prospective case series which included three patients with
four SCCs [2], one retrospective case series in which there was one eligible patient with SCC [3], and the remainder were case reports of one or two patients [4-10].

Outcomes after treatment for these studies are summarised in table 12.

Post-treatment complete response was observed in all patients in eight of the studies (comprising 12 patients)[2-5, 7-10] with histological confirmation of clearance in all but one study[3]. One case report of topical Imiquimod use observed no response in one of three foot and lower leg cSCCs in the same patient[6]. All the studies apart from one[8] followed patients for recurrence for varying periods ranging from 6 months to 4 years, with no reported recurrences. None of the studies reported on deaths attributable to disease.

Skin irritation was commonly reported[2-5, 8, 9], with chemical conjunctivitis reported in one patient with periocular SCC[3] No systemic adverse events were reported.

5-Fluorouracil (5-FU)

We found four studies in which single agent 5-fluorouracil was used to treat eligible SCCs, two of which related to intralesional treatment [11, 12] and two to topical administration of 5-FU [13, 14](Table 13).

There was one prospective multi-centre pilot study (23 patients) which evaluated intratumoral 5-FU, with histologically confirmed clearance in 22 patients (96%) 16 weeks post treatment [11]. Recurrence was not assessed. A case report of intralesional 5–FU reported no recurrence 5 months after treatment[12].

One series of 33 patients with 53 SCCs reported complete post-treatment regression of tumour in 42 cSCCs (79%) treated with up to three courses of 5%, 10% or 20% topical 5-FU, of which 27 (64%) were confirmed histologically. The remaining SCCs regressed partially (15%) or progressed (6%). No recurrences were observed in those who were disease-free at least 1 year after treatment[14]. Another series which only included patients with xeroderma pigmentosum reported superficial regression in 7 of 10 patients
with multiple SCCs, although the number of lesions assessed was not specified. Residual
tumour remained in the deep dermal layer in 4 of 5 patients biopsied and recurrence was
not assessed. Four of the ten patients reported improved quality of life, although this
was not formally assessed[13].

None of the studies reported deaths attributable to SCC.

Cosmetic outcome was reported in one study of intralesional 5-FU, with physicians rating
cosmetic outcome as good to excellent in 91% of cases, slightly lower than the 100%
good to excellent rating of patients[11]. This study reported superficial erosions in 19 of
the 23 (83%) patients, and necrosis in 9 (39%), which cleared after several weeks, plus
local temporary alopecia around scalp lesions. No systemic adverse events were noted in
any of the studies.

**Interferon**

There were four case series that reported outcomes after intralesional administration of
interferon at varying total doses [15-17] [18], the details of which are summarised in
table 14. The largest prospective multi-centre series reported histologically confirmed
 clearance in 24 of 27 (89%) SCCs in actinically damaged skin, but did not assess
recurrence as the site was excised after 18 weeks[15]. A small prospective series
observed histologically confirmed clearance at 3 months in all three included patients
with lower leg SCCs, but again recurrence was not assessed[16]. One case series [17]
reported recurrence of an ear SCC 4 years after treatment with human natural leucocyte
IFN in one of 24 patients, although it was unclear how many patients had appeared to
respond initially to treatment and what became of those who failed to show a complete
response. No recurrence was seen after 23 months in the one patient with an ear SCC
who was included in a series of NMSCs treated with intralesional IFN[18],
None of the included studies reported on deaths attributable to SCC.
One study evaluated cosmetic outcome, with both patients and clinicians rating the appearance as excellent or very good for 93% of lesions treated, and the remainder being rated as either good or satisfactory\cite{15}

Adverse events were described in three studies\cite{15, 16, 18}, with flu-like symptoms and transient derangement of liver function being the most commonly reported events. Depression of mood and reversible dose-related bone marrow suppression were also reported, Severe adverse events causing disruption of daily activity were reported in 10% of all 48 patients treated in 1 study, although none were dangerous or lasting\cite{15}.

**Retinoids**

Oral 13-cis-retinoic acid (0.3-0.5mg/kg/day) was administered with calcitriol (1,25-dihydroxyvitamin D$_3$) (0.5-1 microgram/day) for 3 to 14 months in a prospective series which included six patients who between them had 27 previously untreated histologically proven SCCs at various sites and who were selected on the basis of them being unsuitable for standard local therapy due to the multiplicity of their lesions and their location \cite{19}. Treatment was stopped at 3 months in one of the six patients due to lack of response. One patient had ‘complete regression’ (assessed by clinical reduction in lesion size but not assessed histologically) of their three SCCs at 15 months, and the remaining four patients had partial reduction in tumour size of between 30 and 85% although it was unclear at what time point this response was assessed and some of patients had remained on treatment. All patients treated had mild skin and mucosal reactions, with more pronounced inflammation and crusting of the scalp in three male patients which improved with antibiotic ointment. Two patients also had a transient slight increase in serum triglycerides, and two others had a transient increase in urine calcium, all of which resolved when the dose was decreased. No SCC-related deaths were reported.
There was one case report of the use of single agent oral isotretinoin (13 cis-retinoic acid) given at a dose of 2mg/kg/day for 6 months in a patient with multiple cutaneous SCCs of the legs [20]. Although the number of treated lesions was not specified accurately, one lesion of ‘approximately’ 20 SCCs remained after 6 months and was reported as a keratoacanthoma when examined microscopically after excision. None of the regressed lesions recurred during the 36 months after treatment, although three new SCCs arose in previously unaffected areas. There was no mention of adverse events in this study.

Other treatments

Cetuximab

We found one case report of the use of cetuximab (a monoclonal antibody which binds to the epidermal growth factor receptor [EGFR]) in combination with γ-irradiation to treat a large unresectable 12cm SCC of the temple [21]. Cetuximab was given 24 hours pre-irradiation at a dose of 400mg/m² and in 200mg/m² infusions at weekly intervals throughout the irradiation (total radiation dose 45 Gy). By 4 weeks post treatment the tumour was regressing, and although histologically confirmed tumour was still present at 8 months it had decreased in size to 0.2 x 1.0cm and was excised surgically, with no evidence of further spread 14 months after treatment. The treatment was well tolerated with a follicular-pustular exanthema which healed quickly with corticosteroid therapy.

Combination systemic treatments

Treatment of eligible SCCs with various combinations of drugs was described in five studies [22-26]. These were generally small case series with only a small number of patients with eligible SCCs, or case reports, and are summarised in table 15. In all of the studies definitive initial treatment with surgery or radiotherapy was not possible. Different chemotherapy regimes and modes of administration were used in each study, with follow-up ranging from 8 months to over 7 years. One study reported limb salvage
in two patients after hyperthermic limb perfusion with chemotherapy, with amputation in a third patient with progressive disease after treatment[23]. Of three patients with SCCs of disfiguring size who were treated with neoadjuvant chemotherapy prior to surgery, complete response was seen in two patients, although one of them had a local recurrence of tumour after 8 months, and no response was seen in one patient who died from their disease 10 months after treatment[24]. No recurrences or metastasis were reported in the remaining studies, although these were all single case reports[22, 25, 26]. All of the studies reported adverse events related to chemotherapy. Two treatment related deaths were reported: one of 15 patients had multiorgan failure after hyperthermic isolated limb perfusion[23], and one of 14 died from a pulmonary infection superimposed on lung fibrosis following neoadjuvant chemotherapy[24].


Florez A, Feal C, De La Torre C, Cruces M. Invasive squamous cell carcinoma treated with imiquimod 5% cream. Acta Derm Venereol 2004;84(3):227-8


Skopinska M, Majeski S, Bollag W, Jablonska S. Calcitrol and isotretinoin combined therapy for precancerous and cancerous skin lesions. J Dermatolog Treat 1997;8:5-10


<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study (N=eligible patients)</th>
<th>Dose</th>
<th>Initial response</th>
<th>Follow-up</th>
<th>Recurrence</th>
<th>Adverse events</th>
<th>Cosmesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peris 2006</td>
<td>Open-label trial (3 patients/4 SCCs (temple, inner canthus, leg, forehead), all unsuitable surgical candidates)</td>
<td>Once daily/5x per week/ 8-12 weeks</td>
<td>4/4 complete clinical regression. No histologically evidence tumour on post-treatment biopsies.</td>
<td>Mean 25 months (range 24-27 months)</td>
<td>None</td>
<td>Erythema (3/3); erosion (2/3); pruritus (3/3); burning (1/3); hypopigmentation (1/3); ulceration (1/3). No systemic adverse events.</td>
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<tr>
<td>Ross 2010</td>
<td>Retrospective case series (1 SCC of upper eyelid)</td>
<td>5x/week initially, decreased to 2x/week due to irritation and chemical conjunctivitis</td>
<td>Complete clinical regression at 3 months (not confirmed histologically)</td>
<td>6 months</td>
<td>None in 6 months</td>
<td>Skin irritation and chemical conjunctivitis resolved when frequency of application decreased</td>
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<tr>
<td>Eklind 2003</td>
<td>Case reports (2 renal transplant patients – temple and sternum)</td>
<td>Self-applied 3x per week/12 weeks</td>
<td>Pt 1. No evidence of SCC on 6 month biopsy</td>
<td>6 and 8 months</td>
<td>None at 6/8 months</td>
<td>Pt 1. Some scaling and scar at initial site at 16 weeks. Pt 2. Encrusted and inflammatory erythema 5 wks post treatment. Erythema at week 12 gradually subsiding</td>
<td>-</td>
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<tr>
<td>Florez 2004</td>
<td>Case report (SCC of leg, surgery refused)</td>
<td>Under occlusion every other day for 8 hours/8 weeks</td>
<td>No histological evidence of SCC in excised residual papule at 2 months</td>
<td>12 months</td>
<td>None</td>
<td>Local erythema, superficial erosive changes, discomfort. No systemic adverse eventss.</td>
<td>-</td>
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<tr>
<td>Konstantopoulou 2006</td>
<td>Case report (1 patient/3 SCCs foot and lower leg, surgery refused, radiotherapy considered poor option)</td>
<td>3x per week for 8-12 hours initially then increased to 5x per week/19 weeks or no clinical evidence of residual tumour at sites showing response</td>
<td>Complete clinical response in 2/3 SCCs at 2 weeks with no histological evidence of invasive SCC on biopsy. One SCC failed to respond (excised)</td>
<td>16 months</td>
<td>No recurrence in 2 SCC showing complete response initially</td>
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<td>-</td>
</tr>
<tr>
<td>Study</td>
<td>Description</td>
<td>Duration</td>
<td>Recurrence</td>
<td>Adverse Events</td>
<td>Notes</td>
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<tr>
<td>Martin-Garcia 2005</td>
<td>Case report (nasal SCC, surgery refused)</td>
<td>12 weeks</td>
<td>No recurrence</td>
<td>-</td>
<td>Complete clinical disappearance confirmed histologically 2 weeks post treatment</td>
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<tr>
<td>Nouri 2003</td>
<td>Case report (invasive superficial SCC of nasal tip, other treatments refused)</td>
<td>4 weeks</td>
<td>No recurrence</td>
<td>Irritation and crusting midway through treatment necessitating treatment break. No visible erythema post treatment.</td>
<td>'Cosmetically pleasing' - no fibrosis, scarring, discoloration, residual erythema</td>
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<tr>
<td>Oster-Schmidt 2004</td>
<td>Case reports (2 patients with ear lobe and upper leg SCCs unsuitable for surgery)</td>
<td>21 months and 8 months</td>
<td>No clinical evidence of recurrence at 21 months or 8 months (patient died of unrelated cause)</td>
<td>No adverse events</td>
<td>'Remarkable improved cosmetic result'</td>
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<tr>
<td>Oster-Schmidt 2005</td>
<td>Case report (1 patient, SCC of back of hand, other treatments refused)</td>
<td>4 years</td>
<td>No recurrence</td>
<td>Oedema and mild burning. No systemic adverse events.</td>
<td>'Excellent'</td>
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</table>

Table 1 Studies and outcomes for topical Imiquimod
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study (N=eligible patients)</th>
<th>Dose</th>
<th>Initial response</th>
<th>Follow-up</th>
<th>Recurrence</th>
<th>Adverse events</th>
<th>Cosmesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intralesional 5-FU</strong></td>
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<tr>
<td>Kraus 1998</td>
<td>Prospective multi-centre open label pilot (23 evaluable patients with SCCs confined to upper half of reticular dermis)</td>
<td>Intratumoral FU/epinephrine at 1ml (30mg)/lesion/week at weekly intervals for up to 6 treatments. Mean cumulative dose 3.7ml (range 0.6-6ml)</td>
<td>22/23 histologically confirmed clearance</td>
<td>16 weeks (treated area completely excised)</td>
<td>Not assessed</td>
<td>19/23 (82.6%) superficial erosions, 9/23 (39.1%) necrosis, clearing several weeks after last treatment. Localised temporary alopecia around treated scalp lesions No clinically sig systemic reactions or adverse events</td>
<td>Clinician assessed – 91% ‘good’ to ‘excellent’. Patient assessed – 100% ‘good’ to ‘excellent’</td>
</tr>
<tr>
<td>Morse 2003</td>
<td>Case report, SCC nasolabial fold</td>
<td>Intralesional 5-FU. 0.8-2.4ml once per week for 8 weeks. Total dose 12.8ml</td>
<td>No residual SCC after 8th injection</td>
<td>5 months</td>
<td>None</td>
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<tr>
<td><strong>Topical 5-FU</strong></td>
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<tr>
<td>Hamouda 2001</td>
<td>Prospective cohort of XP patients with multiple facial SCCs (N=10)</td>
<td>Twice daily topical application. Mean treatment duration 6 months (range 2-36 months)</td>
<td>7/10 superficial regression. Of 5 patients biopsied post-treatment, 1 had no residual tumour, 4 had persistent tumour in deep dermal layer</td>
<td>Every 2 months. Mean not specified</td>
<td>Not assessed</td>
<td>Well tolerated, some cases of pruritus with erythema</td>
<td>8/10 crust disappearance and tumour decrease. 4/10 improved quality of life</td>
</tr>
<tr>
<td>Litwin 1972</td>
<td>Prospective (?) cohort (33 patients with 53 SCCs)</td>
<td>Topical 5-FU (5%,10% or 20%), once daily or twice daily. Av treatment time 10.2 weeks (5-37). 79.2% had 1 course, 17% 2 courses, 3.8% 3 courses</td>
<td>42/53 (79%) complete post-treatment regression (64% confirmed histologically). 8/53 (15%) partial regression. 3/53 (6%) progression of SCC</td>
<td>Average 23.2 months (range 3-48 months)</td>
<td>None in those free of disease at least 1 year after completion of treatment</td>
<td>Pain in lesions overlying cartilage</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2 Studies and outcomes after 5-fluorouracil
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Dose</th>
<th>Initial response</th>
<th>Follow-up</th>
<th>Recurrence</th>
<th>Adverse events</th>
<th>Cosmesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards 1992</td>
<td>Prospective multicentre open label trial, 27 SCCs in actinically damaged skin</td>
<td>Intralesional IFN-alfa-2b, as many injections of 1.5 million units as required to blanch tumour &amp; small margin of normal looking skin 3x per week/9 treatments</td>
<td>24/27 (88.9%) histological clearance</td>
<td>18 weeks (site excised)</td>
<td>Not assessed</td>
<td>65% (of all 48 in trial) had &gt;1 adverse event - myalgias, headache, fever. Rigors, flu-like symptoms. 10% severe adverse event causing interruption of daily activity but none dangerous or long-lasting. 14.6% mildly ↑ liver function tests. 6.2% ↓ granulocyte count. 4.2% ↓ platelet count</td>
<td>Patient assessed: 76.9% excellent, 15.4% very good, 3.8% good, 3.8% satisfactory, 0% poor. Clinician assessed: 76.9% excellent, 15.4% very good, 7.7% good, 0% satisfactory, 0% poor.</td>
</tr>
<tr>
<td>Wickramasinghe 1989</td>
<td>Prospective series, 3 patients with SCC, lower leg</td>
<td>Intralesional recombinant IFN-α-20 0.9 million units 3x per week/3 weeks</td>
<td>3/3 Complete clinical response confirmed histologically</td>
<td>3 months</td>
<td>Not assessed</td>
<td>Transient local discomfort at site. Depressive mood in 1 of total of 19 patients in series</td>
<td>-</td>
</tr>
</tbody>
</table>
| Ikic 1995     | Retrospective (?) series, 28 patients with eligible SCCs | a) Human natural leucocyte IFN (HNLI) 400,000-1.2 million units/12-13 applications/3-6 weeks. Total 5.6-21.6 million units  
or  
b) Recombinant IFN-α2c (rIFN) 2-5 million units/20 applications/4 weeks. Total 40-100 million units. | a) 'Complete response' in 32 of 52 patients (all SCCs in series). Unclear if remainder were partial/non responders and what became of them.  
b) Initial response not reported for rIFN treated | Unclear                              | a) 1/24 (ear SCC at 4 years) | -                                                                            |
|              |                          |                                                                      |                                       |                        | b) 0/4 over 3-7 years | -                                                                            |
| Kim 2004     | Case series including 1 patient with ear SCC | Intralesional IFN-α2b 2 million units/3x per week/3 weeks. Total 18 million units | -                                    | 23 months              | No recurrence       | Influenza-like symptoms, short-term neurologic effects (dizziness, |
|              |                          |                                                                      |                                       |                        |                  |                                                                               |
parasthaesia, weakness, confusion, dysarthria, short-term memory loss. Depression at higher doses, transiently elevated LFTs, reversible dose-related bone marrow suppression.

Table 3 Studies and outcomes after interferon
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study ((N=\text{eligible patients}))</th>
<th>Treatment details</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujisawa 2006</td>
<td>Case report (76 year old, non-metastatic SCC of cheek, complete resection too difficult)</td>
<td>IV cisplatin 4mg/m(^2)/day on days 1-5, plus 5-FU 400mg/m(^2)/day for 7 days, with concurrent external beam radiotherapy 2Gy/day 5x per week, total dose 64Gy</td>
<td>No recurrence or metastasis during follow-up</td>
<td>5 years</td>
<td>Mild grade 1 myelosuppression. Ulcer resolving within 3 months</td>
</tr>
<tr>
<td>Olieman 1999</td>
<td>Prospective series (3 patients with locally advanced eligible SCCs of limbs, curative resection not possible without severe mutilation or impaired function)</td>
<td>Hyperthermic isolated limb perfusion – subcut rIFN(^\gamma) 0.2mg od for 2 days prior to 90 min infusion of 0.2mg IFN(^\gamma) plus 3mg (arm) or 4mg (leg) of TNF(^\gamma) &amp; 10-13mg/I melphalan under 39-40(^\circ)C hyperthermic conditions with excision at 6-8 weeks if possible</td>
<td>1/3 complete response (no viable tumour cells); 1/3 partial response; 1/3 local progressive disease and regional disease at 2 months post treatment (then unavailable for follow-up) Limb salvage in 2 patients with complete or partial response. Amputation in patient with progressive disease.</td>
<td>Mean 43 months for 2 patients available for follow-up</td>
<td>Multiorgan failure, deep infection, septic shock and death in 1 of all 15 patients. 1/15 superficial wound infection</td>
</tr>
<tr>
<td>Sadek 1990</td>
<td>Prospective series (3 patients with eligible SCCs of disfiguring size)</td>
<td>Neoadjuvant chemotherapy: cisplatin 100mg/m(^2) day 1, 5-FU 650mg/m(^2) by continuous IVI during 5 days, bleomycin 15mg IV day1 then 16mg/m(^2)/day continuous IVI during 5 days. Repeated every 3-4 weeks for 2-3 cycles. Followed by surgery or interferon (not specified when in relation to chemotheraphy)</td>
<td>2/3 complete response, 1/3 no change (Died of disease at 10 months). Local recurrence after apparent CR in 1/2 at 8 months. disease in 1</td>
<td>8,10 and 22+ months</td>
<td>Pulmonary infection superimposed on fibrotic lung and death in 1 of all 14 patients. Nausea and vomiting in all patients. Grade 3/4 haematologic abnormalities in 4/14. Transient trophic and pigmented bleomycin related skin changes.</td>
</tr>
<tr>
<td>Sheen 2003</td>
<td>Case report (SCC big toe, amputation refused)</td>
<td>Intra-arterial MTX 50mg/d infusion for 8 days plus IM leucovorin 6mg 6hourly for 8 days, then intermittent arterial infusion of 50mg of MTX weekly until wound healed</td>
<td>Complete response 2 months after start of treatment (mass disappeared). No recurrence during follow-up</td>
<td>7 years 3 months</td>
<td>Generalised skin rash and grade 1 itch</td>
</tr>
<tr>
<td>Tantranond 1992</td>
<td>Case report (SCC of pinna, surgery not indicated as bone involvement, radiotherapy doses prohibitive)</td>
<td>Topical 5-FU plus IV cisplatin 60mg/m(^2) on day 1 plus IV 5-FU days 1-4 plus oral isotretinoin 50mg/bd. 6 cycles in total every 28 days</td>
<td>No evidence of residual SCC after 5(^\text{th}) course. No recurrence during follow-up</td>
<td>2.5 years</td>
<td>Isotretinoin discontinued after 60 days due to severe cheilitis</td>
</tr>
</tbody>
</table>

**Table 4: Studies and outcomes – combined chemotherapy regimes**