

Editor's note:

“Palliative Radiotherapy Column” features articles emphasizing the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L. W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles and perspectives relating to palliative radiotherapy, editorials and commentaries on recently published trials and studies.

Review Article on Palliative Radiotherapy

Palliative radiotherapy for skin malignancies

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Abstract: Palliative radiotherapy (PRT) improves patient quality of life (QoL) through alleviating cancer-associated symptoms such as pain, bleeding, and ulceration. Palliative management of patients with skin malignancies requires consideration of cosmetic and psychosocial outcomes as QoL measures. In this review, we highlight the current literature and advances in the use of PRT for patients with the three most commonly encountered forms of skin malignancies: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. The disease course and sensitivity to radiation varies, thus dictating the palliative goal and scheduling for PRT.

Keywords: Palliative radiotherapy (PRT); skin cancer; basal cell; squamous; melanoma

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Introduction

Skin cancer is the most prevalent cancer in the United States (1,2). Early intervention may even be curative for patients with either basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) subtypes, which respectively constitute approximately 70–80% and 20% of non-melanoma skin cancers (NMSC) (3,4). Additionally, early detection of melanoma and surgical excision with Mohs micrographic surgery (MMS) can achieve a 5-year overall survival of 97% in stage I patients, while the rate markedly decreases to

15–20% in those with distant metastatic disease (5). Despite advances in new treatments for melanoma, it still accounts for 70–90% of all skin cancer-related deaths (3,6).

Palliative care, as defined by the World Health Organization, includes improving patient quality of life (QoL) and relieving symptomatic distress (7). In the context of skin cancer, palliative care may address many patient concerns including physical tumor-related pain, psychosocial distress from being in public with visible disease, increased time spent in a health-care environment for care, and

financial costs (8-13). It is with these factors in mind that treatment selection for advanced skin malignancies must incorporate patient goals and preferences.

The focal point of the localized treatment landscape in skin cancer revolves around surgical intervention. For BCC and SCC, the primary local therapies include MMS, cryotherapy, radiation therapy (RT), and curettage and electrodissection (C&E) (14,15). Other therapies such as imiquimod, cryosurgery, or photodynamic therapy only target the superficial skin and are indicated for patients who choose not to undergo surgery or radiation. For melanoma, surgical excision is also the mainstay for primary localized melanoma, however topical imiquimod or radiation may be used as an alternative depending on tumor location and patient comorbidities (16). In the rarer NMSCs such as Merkel cell carcinoma (MCC) and dermatofibrosarcoma protuberans (DFSP), surgical approaches remain the primary mainstay of treatment (17-22). MCC and DFSP are highly-recurrent cancers (median time to recurrence; MCC: 5.5–16.5 months, DFSP: 1–2 years) and often require a wide surgical margin (up to 4 vs. 2 cm in melanoma and 1 cm in BCC/SCC) that may result in disfiguring post-operative scarring (17-19,21). In light of the varying treatment considerations, we herein provide a focused review of the role of RT as a palliative modality in BCC, SCC, and melanoma.

RT with palliative intent is directed towards improving QoL rather than aiming to cure a patient of their advanced disease (23). In particular, radiation may be used to control cancer-related bleeding, pain, ulcerations leading to infections, and neurological dysfunction (24). Palliative radiotherapy (PRT) may be recommended for patients who have poor performance status, inoperable tumors, and who are otherwise poor candidates for more extensive procedures (25). Palliative treatment should be short-duration for those patients who have a poor prognosis, or are unable to travel for multiple treatments (24). High local control rates may also alleviate patient concerns regarding disease recurrence. With regard to skin cancer, the side effects of RT may manifest as subdermal fibrosis, desquamation, erythema, hypopigmentation, epidermal atrophy, and telangiectasia (26). For the purposes of this review, we have preferentially included studies on palliative RT for skin cancer based upon direct mention of cosmetic outcomes, skin-related side effects from RT that may be used as a surrogate for cosmetic outcome, or more hypofractionated schema.

Methods

Studies related to PRT use in skin cancer were independently identified and evaluated by J Lin and W Vuong from existing literature. Authors included studies pertaining to radiotherapy for skin cancer that addressed any of the following criteria in order of importance: (I) mention of palliative outcomes including cosmesis, pain and other cancer-related symptomatic relief, or comfort; (II) mention of skin-related side effects that may be used as a surrogate for cosmetic outcome; (III) use of fewer than 15 fractions for total treatment. Due to the scarcity of research solely focused on palliative results, studies that used total treatment doses thought of as radical treatment but reported palliative outcomes were considered for inclusion. Sample size, total dose, fraction size, number of treatments, local control, and toxicity were obtained from the published articles.

Results

BCC and SCC

Of the studies screened for PRT in BCC and SCC that matched one of the three criteria listed above, nine were selected as representative studies. Sample sizes ranged from 28 to 1,166 patients in various anatomical locations in the head and neck region as well as the extremities. Common fractionation schemes include 3 to 10 fractions with dose per fraction sizes ranging from 7 to 10 Gy (*Table 1*).

Cosmetic outcomes from EBRT, based upon the presence of telangiectasia, pigment change, and fibrosis, are reported to be generally satisfactory if not excellent in patients with localized disease (>90% with at least a satisfactory outcome) (27-29,31). In general, fractionated approaches have been employed to reduce skin toxicity while maintaining a high treatment dose to the lesion of interest (*Table 1*) (25,27-31). Early comparisons examined the side effect profile of a large dose at once (20–22.5 Gy in 1 fraction) versus more fractionated schemes including 40–45 Gy over 10 fractions, or 45–50 Gy in 15 fractions (*Table 1* for full listing of schema) (27). Despite the heterogeneous treatment regimens, side effects were limited to fewer than 10% of patients (range, 3–9.6%) and were primarily related to telangiectasia, pigmentation, fibrosis, and treatment-field ulceration (*Table 1*). Side effects were more commonly found in patients with larger tumors (≥ 5 cm) or that received higher doses per fraction, although local control rates

Table 1 Select studies evaluating local control and/or cosmetic outcomes in BCC and SCC of the eyelid, head and neck, and extremities

Authors	Anatomical location	Sample size	Treatment (electron versus photons)	Total dose range	Dose per fraction	Local control	Long term complications	Misc (tumor size <2 cm, etc.)
Fitzpatrick <i>et al.</i> , 1984 (27)	Eyelids	1,166	Photon	Single treatment of 20 or 22.5 Gy (n=296); 35 or 40 Gy in 5–7 days (n=524); 10 consecutive fractions totaling 40–45 Gy in 2 weeks (n=260); 15 fractions totaling 45–50 Gy in 19 days (n=45); 50–60 Gy over 4–6 weeks (n=41)	3–20 Gy	>90% for both BCC and SCC at 5 years	9.6% had significant side effects: erythema, moist desquamation, crust formation; hypopigmentation; conjunctivitis; cataracts; keratitis; epiphora following ectropion; skin atrophy with telangiectasia	–
Abbatucci <i>et al.</i> , 1989 (28)	Face (excluding lips, ears, eyelids)	742	Photon	30.6 Gy in 3 fractions in 14 days (n=675); 40.20 Gy in 6 fractions in 35 days (n=17)	6–10 Gy	95.85% at 2 years	3% had complications: severe watering of the eye (lacrimal obstruction)	Complications closely correlated with the irradiated surface and volume; nasal locations had highest incidence of recurrence; 97% satisfactory cosmetic outcome
Locke <i>et al.</i> , 2001 (29)	Head/neck, limbs	468	Electron (19%), X-rays (60%), combination (20%), photons (<2%)	Varied treatments: <40 to >60 Gy	<2 to >4 Gy	–	Overall complication rate =5.8%; mostly soft-tissue necrosis	Local failure was related to the daily dose fractionation; 89% local tumor control reported (length of time not included to this value)
Ferro <i>et al.</i> , 2015 (30)	Head (n=30); lumbar (n=1) (excluded T3–T4)	31 (all ≥70 years old)	Electron or photon	30 Gy for 6 consecutive days	5 Gy	94.1% (BCC) and 90.9% (SCC) at 2 years	Acute: skin toxicity, mucositis; late: hyperpigmentation, skin atrophy, fibrosis	–
Cognetta <i>et al.</i> , 2012 (31)	Head	1,149	X-ray	35 Gy (5 fractions) 3 times a week for a total of 5–7 treatments	7 Gy	~95%	Hypopigmentation, telangiectasias	–
Barnes <i>et al.</i> , 2010 (25)	Head, neck, chest, thigh, hand	28	X-rays, electrons or photons	24 Gy (3 fractions) on days 0, 7, and 21 over 3 weeks	8 Gy	–	No late side-effects reported	82.6% relief of distressing symptoms, 78.3% overall response rate

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

were similar between fractionation schedules. Additionally, fractionation schemes of 30 Gy in 6 fractions, 35 Gy in 5 fractions, and 24 Gy in 3 fractions have been utilized (*Table 1*) as a balance of minimizing dose-related toxicity through fractionation while not excessively burdening patients with long courses of radiation. Local control rates are generally excellent, ranging from conservative estimates of 93.3–95% in those treated with superficial orthovoltage (X-ray) radiation (27,29,31). One particular series reported that overall local control rates were lower in patients receiving electron beam RT (29).

Direct comparisons of cosmetic outcomes between surgical intervention and RT are rare; however, it has been suggested that surgery may outperform RT regarding long-term cosmetic results (87% *vs.* 69% “good” evaluation, 4-year follow-up) (32). BCC patients with <4 cm wide lesions were randomized to surgery or PRT, but it must be noted that only 20 of the RT patients underwent conventional EBRT while other patients had either interstitial brachytherapy or contact therapy (32). More modern evaluations of brachytherapy alone have reported excellent cosmetic outcomes (33). Specifically, an “excellent” response was reported in 94.2% and a “good” response in 3.3% of lesions treated with high-dose-rate electronic brachytherapy based upon the RTOG/EORTC Late Radiation Morbidity Scoring Schema (34).

In addition to cosmesis, PRT may relieve initial presenting symptoms associated with NMSC. Symptoms including pain, bleeding, odor, and/or discharge were successfully palliated in 61.3% of symptomatic lesions or 82.6% of accessible sites by last follow-up using a schedule of 21 Gy in 3 fractions on days 0, 7, and 21 (25). SCCs and BCCs also have a small risk of invading perineural tissue (2.5–14%) which may cause pain (35). Unfortunately, only a small proportion of patients with locally-controlled, perineurally-invasive disease experienced symptomatic relief after PRT. Median RT doses of 70 Gy in 39 fractions obtained a 5-year local control rate of 55% (BCC) and 57% (SCC) in clinical perineural invasion cases, and only 7% of the patients had any symptom relief after successful local control (8).

Melanoma

Ten studies that met one of the three criteria enlisted in the “Methods” section were selected as representative studies. Reports were primarily in the metastatic setting with patient sample sizes ranging from 14 to 466 being treated with

total doses ranging from 20 to greater than 60 Gy (*Table 2*) (36–44). The studies had a variety of anatomic locations treated including cutaneous and lymphatic tissue of the head and neck, thorax, abdominal, and groin regions as well as brain (*Table 2*).

Melanoma has had a historical reputation for radiation resistance; however, a growing body of clinical evidence has shown that it has a higher repair capacity and is more susceptible to larger doses of radiation per treatment fraction (*Table 2*). Initially, comparisons of scheduling 32 Gy in 4 fractions versus 50 Gy in 20 fractions demonstrated higher toxicity than in the 32 Gy ×4 fractions arm with equivocal remission rates (*Table 2*) (36). Notably, patients were randomized without controlling for tumor size or volume. A separate evaluation of 204 lesions demonstrated that complete response rates were significantly associated with fraction size (24% *vs.* 57% in fractions of <4 *vs.* ≥4 Gy respectively, $P < 0.001$) and that controlling for tumor size resulted in more accurate estimates of total delivered radiation through the extrapolated total dose measure (44). Similarly, patients receiving a total dose greater than 30 Gy have a longer, durable response (7 *vs.* 4 months for treatments of <30 Gy) (45). Associated clinical toxicities are similar with PRT use in BCC and SCC for cutaneous lesions and include ulceration, atrophy, telangiectasia, moist desquamation, and erythema (*Table 2*). However, palliation of nodally-metastatic lesions incurs a risk of lymphedema at rates of 30–58% depending on location (*Table 2*).

Discussion

Managing malignancies of the skin requires comprehensive QoL evaluation including post-treatment cosmesis and psychosocial stress that must be weighed against clinical outcomes. The majority of skin cancer patients are treated with surgery, although radiation also offers a high degree of tumor control while preserving patient cosmesis. Our review sought to highlight the current evidence for use of PRT in skin cancer including BCC, SCC, and melanoma.

Cosmetic outcomes were generally satisfactory based upon patient perception and objective measures such as skin-related toxicities as reported by the RTOG/EORTC guidelines. In the context of BCC and SCC, the use of varying fractionation schemes did not significantly affect local control although the dose per fraction size influenced toxicity rates. Thus, schema should try to maximize treatment-dose while minimizing toxicity, meaning fewer fractions should be used. This translates to ranges of 24–

Table 2 Select studies evaluating palliative RT in melanoma in cutaneous, nodal, and brain metastatic lesions

Authors	Anatomical location	Sample Size	Treatment (electron versus photons)	Total dose range	Dose per fraction	Local control	Long term complications	Misc (tumor size <2 cm, etc.)
Sause et al., 1991 (36)	Soft tissue, nodal, other (excluded CNS and abdominal)	126	Electron and photon	32 Gy (4 fractions) once a week for 21 days; 50 Gy (20 fractions) 5 times a week for 26–28 days	2.5 vs. 8 Gy	–	Ulceration (n=3), atrophy, telangiectasia (n=3)	Toxicity slightly greater in 4x8.0 Gy arm; larger doses did not have greater response
Overgaard et al., 1985 (37)	Lymph and cutaneous (groin, leg, back, axilla, thorax, arm, abdomen)	14	Electron and photon	27 Gy (3 fractions) or 40 Gy (8 fractions) twice weekly	5 vs. 9 Gy	–	Moist desquamation (14%), moderate erythema (43%), severe erythema (34%)	No difference found between the two treatments; responses lasted >4 months in all treatments
Chang et al., 2006 (38)	Lymph and cutaneous (head/neck, axilla, upper torso, groin, upper extremity)	45	–	600 cGy (5 fractions) twice per week for 2.5 weeks; 200 cGy daily dose (~30 days)	120 vs. 600 cGy	87% at 5 years	Acute parotitis, osteoradionecrosis, radiation plexopathy	Hypofractionation vs. standard fractionation (600 cGy fractions)
Ang et al., 1994 (39)	Cutaneous (head and neck)	174	Electron	30 Gy of 5 fractions twice a week for 2 weeks	6 Gy	88% at 5 years	Neck fibrosis, mild ipsilateral hearing impairment, and transient exposure of external auditory canal cartilage	Hypofractionation
Ballo et al., 2006 (40)	Nodal (cervical, axilla, groin)	466	Electron and photon	30 Gy twice weekly over 2.5 weeks	6 Gy	89% at 5 years	Lymphedema (~30% for patients with groin LN metastases, 5 years rate)	Hypofractionation, lymphedema reported within 5-year follow-up
Stevens et al., 2000 (41)	Primary and nodal (head/neck, limbs)	174	Electron and photon	30–36 Gy in 5–7 fractions over 2.5 weeks (94% received 33 Gy in 6 fractions over 18 days)	4–6 Gy	89% at 5 years	Lymphedema (58% axillary), asymptomatic skin atrophy	Hypofractionation, lymphedema reported with a median follow-up of 30 months

Table 2 (continued)

Table 2 (continued)

Authors	Anatomical location	Sample Size	Treatment (electron versus photons)	Total dose range	Dose per fraction	Local control	Long term complications	Misc (tumor size <2 cm, etc.)
Seegenschmiedt et al., 1999 (42)	Head, neck, upper and lower limbs, nodular, and other sites (vagina, rectum, mucosa)	114	Electron and photon	Median total dose of 48 Gy	2-6 Gy	-	-	21% survival at 4 years
Gaudy-Marqueste et al., 2006 (43)	Brain cortical (n=33); subcortical (n=159); cerebellum (n=16); brainstem (n=5); nuclei (n=7); posterior fossa (n=1)	106 patients (221 BMs)	Photon	Median 25 Gy (50% isodose line used)	-	Actuarial rates were 100% at 3 months, 85% at 6 months, 69% at 1 year, and 69% at 3 years	Intralesional bleeding, intracranial pressure, neurologic deficit, radiation necrosis	-

RT, radiation therapy.

35 Gy in 3 to 6 fractions. In the setting of melanoma, greater fraction sizes have been associated with better outcomes and schedules utilizing at least 4 Gy per fraction for a total dose greater than 30 Gy are recommended. While symptomatic outcomes vary based upon tumor location, PRT can successfully alleviate pain, bleeding, and neurological symptoms. More extensive research is still necessary to fully evaluate the QoL outcomes associated with PRT, particularly in patients treated with current technologies.

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Footnote

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