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Original Research Article

Hypofractionated adjuvant radiotherapy in cutaneous squamous cell and basal cell carcinoma of the head and neck: 50(Gy) in 20 study

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ABSTRACT

Purpose: To assess clinical outcomes and tolerability of patients with cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the head and neck region, treated with adjuvant radiotherapy prescribed to a moderately hypofractionated regimen of 50Gy in 20 fractions.

Methods and materials: Eligibility for this retrospective study included patients with cutaneous SCC and BCC of the head and neck who received adjuvant radiotherapy to a dose of 50Gy in 20 fractions (2.5Gy per fraction) between 1/1/2007 and 31/12/2019 at a tertiary Queensland hospital. Primary endpoint was freedom from local failure (FFLF). Secondary outcomes were loco-regional recurrence-free survival (LRRFS), overall survival (OS) and toxicity rates. Acute toxicities were retrospectively collected and reported according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Results: A total of 126 patients were evaluated in this study with a median follow up period of 19.7 months (interquartile range 1.63–121.03). The median age was 68.3 years old. Twenty-six patients were immunosuppressed. Predominant histopathology was SCC (63.5 %). The majority were staged pT1-2 (74.6 %), and clinically or pathologically N0 (96.8 %). 122 patients received adjuvant radiotherapy to the primary tumour bed, and four patients received treatment both the primary and nodal region. FFLF was 95.8 % and 92.2 % at 2 and 5 years, respectively. No statistically significant clinico-pathological factors were prognostic of FFLF. LRRFS was 90.5 % at 2 years and 83.1 % at 5 years. OS was 88.7 % at 2 years and 69.9 % at 5 years. Five of the 21 deaths were related to the index cutaneous carcinoma. Grade 3 radiation dermatitis and mucositis occurred in 13.5 % and 4.0 % of patients, respectively. There were no grade 4/5 toxicities. Four patients required treatment breaks, of which two were planned breaks. No patient required enteral feeding during their RT course.

Conclusion: This is the largest series to date evaluating a single moderately hypofractionated adjuvant radiotherapy regimen for cutaneous SCC and BCC of the head and neck. This regimen was associated with high locoregional control and was well tolerated. A moderately hypofractionated course of adjuvant radiotherapy in cutaneous SCC and BCC can be a suitable option to reduce treatment duration.

1. Introduction

Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) are the most common malignancy worldwide. They are particularly prevalent in individuals with a significant history of UV exposure, fair skin and immunosuppression. Eighty percent tend to occur in the head and neck region [1].

Adjuvant radiotherapy (RT) to the primary site is an established treatment following surgery to reduce the risk of local recurrence in the presence of high-risk clinico-pathologic features which include positive or close (<5 mm) margins, increasing tumour thickness (>6 mm), large tumours, invasion into surrounding structures such as bone (T3 & T4

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AJCC 8th Edition), perineural invasion, recurrent disease and/or immunosuppression [2].

Although a range of dose fractionation RT schedules have been reported for use in the management of cSCC/BCC, the National Comprehensive Cancer Network (NCCN) guideline on SCC Version 1.2024 recommends 60-60Gy using conventional fractionation of 2Gy/treatment. In the randomized phase III TROG 05.01 trial of adjuvant RT for high-risk cSCC of the head and neck, 60–66Gy in 2Gy/fraction was specified in the protocol [3]. Most of the published data are retrospective series containing a range of radiation dosing, technique and mix of treatment indications, making it difficult for a clinician to select a suitable and safe schedule (Table 1).

The COVID-19 pandemic has led to an international collaborative effort in reinvigorating the focus of utilizing hypofractionated (>2Gy/fraction) regimens to limit patient visits [4]. The use of hypofractionation regimens can often be limited by concerns regarding the increased probability of late effects of adjacent non-skin organs at risk (OAR) and suboptimal long-term cosmesis outcomes such as scarring and hypopigmentation [5]. Despite these risks, select patients, particularly those who reside long distances from the treating hospital or are elderly, find the convenience of fewer treatments and shorter overall treatment lengths appealing [6].

The purpose of this study was to assess the tolerability and clinical outcomes of a cohort of patients treated at our institution with a moderately hypofractionated regimen, 50Gy in 20 fractions as adjuvant treatment for high-risk cSCC and BCC of the head and neck: the *50(Gy) in 20 study*.

2. Materials and methods

This was a retrospective study of patients with cSCC or BCC of the head and neck, treated with adjuvant RT, 50Gy in 20 fractions at our institution between January 2007 and December 2019. Institutional ethics approval was obtained prior to commencement of this study (HREC number LNR/2020/QMS/62043). Patients with only nodal disease at presentation were excluded.

Patients with mucosal SCC, cSCC or BCC not arising from the head and neck, did not receive RT as adjuvant therapy or underwent concurrent chemotherapy were excluded.

Clinico-pathological data collected from the medical records included age, gender, immunosuppression state, date of diagnosis, TNM staging (AJCC 6th – 8th edition dependent on year of presentation), histopathological features, RT details, and cancer control outcomes.

2.1. Study endpoints

The primary endpoint of the study was freedom from local failure (FFLF). Secondary endpoints were loco-regional recurrence-free survival (LRRFS), overall survival (OS) and toxicity rates. Time to event endpoints were calculated from date of histopathological diagnosis to a defined event (local failure, loco-regional failure, death) and censored at last follow-up. The close-out date for the study was 11 May 2020.

Toxicities were retrospectively collected and reported according to Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. During RT, requirement for enteral feeding, unscheduled treatment break or hospitalisation were also recorded.

2.2. Follow-up schedule

The routine departmental practice was for patients to be seen by the treating radiation oncologist or team member on a weekly basis during RT, as well as at 6 weeks following RT. Subsequent follow-up schedules at the hospital was typically every 3–6 months in the first 2 years, then annually for up to 5 years. Imaging was performed if there was suspicion of recurrence or interval development of symptoms.

2.3. Statistical analyses

Descriptive statistics were presented using mean and standard deviation (SD) when data was normally distributed otherwise median, range and inter-quartile range (IQR) when normality was not met. Shapiro-Wilk test was used to assess normality of the data. Categorical variables were described using frequencies and percentages.

The Kaplan–Meier method was used to estimate FFLF, LRRFS and OS. Univariate analysis using a Cox proportional hazards model was performed to identify potential association between clinico-pathological factors and FFLF. Hazard ratios (HR) were reported with 95 % confidence intervals (CI). The proportional hazards assumption in the Cox regression models were tested using the test statistic of Grambsch and Therneau. All analyses were performed using the R statistical software and $p < 0.05$ were considered significant [7].

3. Results

3.1. Study cohort

We identified 242 patients delivered with a prescription dose of

Table 1
Selected publications reporting adjuvant non-melanoma skin cancer treatments.

Author	Definitive (n)	Adjuvant (n)	Dose	Number of fractions	modality	LFFS	LRFFS	OS
<4Gy/#								
Gross Marconi	939	65	50 55 60 Other	20 (273) 20 (185) 30 (419) (144)	kv	BCC: 96 % 5 year SCC: 92 % 5 year	–	–
Tsao	63	31	32.5–64Gy	5–32	Orthovoltage x-rays	90 % at 2 years, 85 % at 5 years	–	75 % at 2 years, 51 % at 5 years (actuarial)
Silva	322	12	17.5Gy–65Gy	1–30	Orthovoltage x-rays	86.6 % 2 year, 79.2 % at 5 years	–	–
Gauden	162	74	36	3	superficial	98 % (median f/u 66 months)	–	–
Van Hezewijk	140 246	18 30	54 44	18 10	e	97.6 % (3 year) 93.6 %	–	–
Arenas	–	32	(45–57) – mean 49Gy	3Gy per fraction	HDR brachy	96.3 % ((3 years DFS, same for 5 year DFS)	–	–
>4Gy/#								
Ferro	–	16	30	5	E + MV photons	93.3 % (2 year)	–	–
Delishaj	45	12	40–50	8–10	HDR brachy	96.5 %	–	–
Valeriani	19	7	60Gy	5–6	E + MV photons	92.3 %	–	95 % 2 year (cancer specific survival)

50Gy in 20 fractions in our database. We excluded 116 patients due to histology (N = 43), non-head and neck site (N = 33), missing RT data (N = 23), RT as definitive treatment (N = 15), RT as palliative treatment (N = 7). The study cohort evaluated included 126 patients.

Within the evaluated study cohort, four patients had primary and nodal disease that required radiotherapy to both sites. Three patients received elective neck irradiation for a clinically node negative neck.

The median age was 68.3 years (interquartile range, (63.5–74.9)). The majority of patients were male (74.6 %). Twenty-six patients (20.6 %) had an immunosuppressive condition (Table 2). The most commonly treated site was the face (28.6 %) (Table 3). The majority of patients had early stage disease, with pathological T1/2 disease (74.6 %) and clinically or pathologically staged N0 disease (96.8 %). There were 4 courses (3.2 %) delivered to node positive disease on neck dissection. Histology was SCC in 63.5 % of the patients evaluated and the most common modality used was electron therapy (71.4 %). Additional tumour and treatment characteristics are detailed in Table 3.

3.2. Treatment outcomes

The median follow-up of alive patients at the study close-out date was 19.7 months (range 1.6–121.0 months). Of the cohort of 126 patients, there were seven local failures detected. The estimated FFLF was 95.8 % (95 % CI 91.8–99.9) and 92.2 % (95 % CI 86.2–98.7) at 2 and 5 years, respectively (Fig. 1). The median time from diagnosis to local failure was 11.6 months (range, 5.4–61.0). The clinico-pathological details of patients who had local failure are detailed in Table 4. Univariate analysis did not identify any statistically significant clinico-pathological factors associated with FFLF (Table 5). Close margin showed a trend to increased local failure, when compared with negative or positive margins.

Five patients in the cohort developed with nodal recurrence. Of these, four were isolated nodal failures, and one patient developed synchronous local and nodal failure. 1 of these nodal recurrences occurred in a patient who presented initially with pN2b disease, and received initial treatment consisting of superficial parotidectomy and ipsilateral neck dissection followed by adjuvant radiotherapy. This patient also developed synchronous metastatic disease at the time of relapse. The other 4 nodal recurrences occurred in setting of adjuvant radiotherapy for initially cN0 disease. However, these were high risk cases due to 3 cases being pT3 on presentation, and 2 receiving surgery requiring local flap reconstruction.

The median time from diagnosis to regional failure was 7.6 months (range, 5.6–17.7). The LRRFS was 90.5 % (95 % CI 84.7–96.7) and 83.1 % (95 % CI 73.3–94.1) at 2 years and 5 years, respectively (Fig. 2).

Two patients developed distant metastases. In one patient, this occurred 14 months following nodal recurrence, at 21.6 months from diagnosis. This patient remained alive at last follow up, following management with neck dissection and immunotherapy. The second patient developed metastasis 63.3 months from diagnosis, without any evidence of local or nodal failure, and died at 64 months following diagnosis, due to malignant pleural effusion and hospital acquired pneumonia.

There was a total of 21 deaths, five were related to the index NMSC, 16 were due to other concurrent comorbidities. The estimated 2 and 5-year OS was 88.7 % (95%CI 82.2–95.7) and 69.9 % (95%CI 57.8–84.7), respectively.

Table 2
Demographics of patient cohort.

Characteristic	Number of patients
Patients receiving adjuvant RT	126
Gender	
Male	94 (74.6 %)
Female	32 (25.4 %)
Median age at diagnosis (IQR)	68.3 (63.5–74.9)
Immunosuppressive condition	
From:	26
- Haematological malignancy	9 (7.1 %)
-Transplant	10 (7.9 %)
-Pharmacotherapy	6 (4.8 %)
-HIV	1 (0.8 %)

Table 3
Tumour and treatment characteristics of the patient cohort.

Characteristic	Number of tumours
Tumours treated with adjuvant RT	126
Pathological T-classification*	
T1	49 (38.9 %)
T2	45 (35.7 %)
T3	26 (20.6 %)
T4	6 (4.8 %)
Pathological N-classification*	
N1	2 (1.6 %)
N2a	1 (0.8 %)
N2b	1 (0.8 %)
Clinically N0	122 (96.8 %)
Histology	
SCC	44 (34.9 %)
BCC	80 (63.5 %)
BCC and SCC	2 (1.6 %)
Site of primary lesion	
Scalp	12 (9.5 %)
Forehead	12 (9.5 %)
Temple	7 (5.6 %)
Face	36 (28.6 %)
Nose	30 (23.8 %)
Ear	18 (14.3 %)
Post-auricular/neck	4 (3.2 %)
Lip	7 (5.6 %)
Perineural invasion	
Single nerve <0.1 mm	33 (26.2 %)
Single nerve ≥0.1 mm	29 (23.0 %)
Multifocal	16 (12.7 %)
Large/named nerve	9 (7.1 %)
Named nerve	39 (30.9 %)
Absent	
Initial vs recurrence	
Initial	105 (83.3 %)
Recurrence	21 (16.7 %)
Margin status	
Positive	33 (26.2 %)
Close (<5 mm)	59 (46.8 %)
Negative	29 (23.0 %)
Unknown	5 (4.0 %)
Wound closure	
Primary closure	10 (7.9 %)
Skin graft	17 (13.5 %)
Flap	22 (17.5 %)
Unknown	77 (61.1 %)
Site of previous RT	
Yes	5 (4.0 %)
No	121 (96.0 %)
RT modality	
Electrons	90 (71.4 %)
3D conformal	25 (19.8 %)
IMRT	1 (0.8 %)
VMAT	10 (7.9 %)

3.3. RT-related toxicities in the adjuvant cohort

Grade 3 toxicities were recorded for dermatitis and mucositis in 13.5 % and 4.0 % of RT courses, respectively. There were no grade 4 toxicities or treatment-related deaths. RT-related toxicities have been detailed in

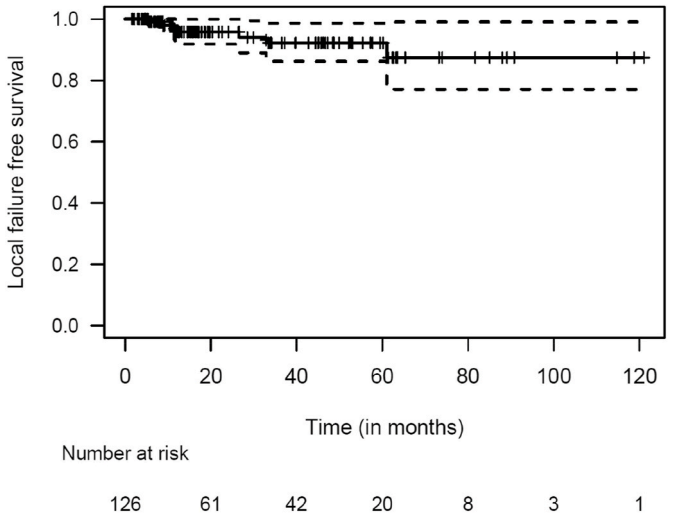

Fig. 1. Kaplan Meier estimates for local failure free survival.

Table 6.

Two patients did not complete RT that were not treatment related causes (both had cardiovascular events). Four patients required treatment breaks: two patients were planned treatment breaks for anticipated toxicity, both involved treatment of the face, and the other two patients were due to causes unrelated to RT (vomiting/diarrhoea, and upper respiratory tract infection). No patient required enteral feeding during their RT course.

4. Discussion

This is the largest study to date evaluating the outcomes of a moderately hypofractionated RT regimen as adjuvant treatment for cutaneous SCC/BCC of the head and neck. The 50Gy in 20 fraction prescription was well tolerated and resulted in a 5-year FFLF of 92.2 %.

Cutaneous SCCs and BCCs are radioresponsive with excellent local control rates >90 % reported following definitive RT utilizing a range of hypofractionated regimens [8–10]. The use of hypofractionation in the adjuvant setting however, is less established particularly for head and neck sites where consideration of non-skin OAR can be as important as skin toxicities when choosing an appropriate dose fractionation schedule. Whilst there is substantial volume of retrospective evidence in respect to patient numbers, with a recent systematic review summarizing 40 publications, the majority of the included series report combined outcomes for radiotherapy used in both the definitive and adjuvant setting, as well as with a heterogenous dose fractionation schedule [9].

Recent meta-analyses that have reported on the efficacy of hypofractionated RT regimens include a significant proportion of non-head and neck sites and adjuvant RT account for <10 % of cases evaluated [8,9]. Table 1 provides a summary of relevant studies for which the number of adjuvant treatments were reported. Our study represents the largest series to date reporting the outcomes following hypofractionated RT in the adjuvant setting for head and neck cutaneous malignancies. Tumours treated in our series are in general, considered to have

Table 5
Univariable analysis of potential clinico-pathological prognostic factors for local failure.

Clinico-pathological factor	Hazard ratio (95 % CI)	p-value
Age >70 vs. ≤70 years	1.8 (0.4–8.1)	0.45
Age (years)	1.1 (0.97–1.1)	0.22
Histology SCC vs. BCC	3.7 (0.45–31)	0.22
Pathological T-category T3/4 vs. T1/2	1.2 (0.24–6.3)	0.82
Initial vs recurrence	1.6 (0.31–8.4)	0.56

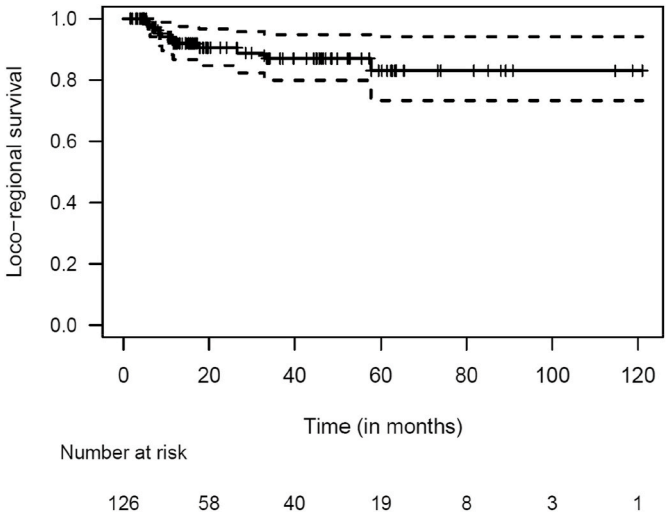

Fig. 2. Kaplan Meier estimates for loco-regional free survival.

Table 4
Clinico-pathological details of patients with local failure.

Patient number	Immune compromised	Site of primary	Histology	Pathological T classification	Clinical N classification	Margin status	Perineural invasion	RT technique	Time to failure (months)	Salvage treatment
1	No	Scalp	SCC	T2	N0	Involved	Single <0.1 mm	electrons	61	nil
2	No	Post auricular	SCC	T2	N0	Involved	multifocal	3d	12	radical neck dissection, pec flap, PORT
3	No	Temple	SCC	T2	N0	Close (<5 mm)	no	electrons	9	Salvage resection
4	Yes	Scalp	SCC	T2	N0	Close (<5 mm)	No	electrons	27	nil
5	Yes	Scalp	SCC	T2	N0	Involved	Single <0.1 mm	electrons	5	WLE, skull burring, scalp flap + PORT 48/20
6	No	Nose	BCC	T4	N0	Close (<5 mm)	no	IMRT	33	Further resection + reirradiation 45/25#. Commenced on Sonidegib for further recurrence
7	No	Face	SCC	T2	N0	Close (<5 mm)	Single <0.1 mm	3D	11	WLE, skull burring, chasing V1 and temporoparietal pericranial flap

Table 6
Acute RT-related toxicities in the adjuvant cohort – treatment course specific.

Acute toxicity	CTCAE v4.03 grading			
	0	1	2	3
Dermatitis	0	31	78	17
Mucositis	99	17	5	5
Pain	115	6	5	0
Dysphagia	122	3	1	0
Conjunctivitis	120	6	0	0
Watering eyes	3	0	0	0
Epistaxis	8	0	0	0
Dysgeusia	5	0	0	0
Nasal congestion	5	0	0	0

sufficiently high risk of needing bimodality therapy due to location, margin status and perineural invasion. NMSC of the head and neck can be difficult to manage with surgical excision alone due to the limited ability of wider margins and the presence of perineural invasion, requiring the need for adjuvant therapy [11]. This is reflected in our cohort, with 92 patients (73.0 %) having either close or positive margins, and 80 patients (63.5 %) with pathologic evidence of perineural involvement.

Skin cancers located in the head and neck also present unique challenges for radiotherapy. Tumours are often located on or close to organs with functional and cosmetic importance. It is common to steer towards using conventional fractionation schedules ie $\leq$ 2Gy per fraction in these sites due to concerns of late toxicity with hypofractionated regimens. However, this is based largely on radiobiologic principle, and not substantiated in the current literature. A meta-analysis of hypofractionated treatments for skin BCC and SCCs evaluating 9729 patients with regards to long-term cosmesis data found no correlation between dose or fractionation and cosmetic outcome [12]. They reported that the majority of patients (92 % of their cohort) reported a 'good' cosmetic outcome for any fractionation regimen. Our study demonstrated a low toxicity profile with total incidence of grade 3 mucositis and dermatitis was 3.67 % and 13.24 % respectively. Late toxicity was seldom identified in the follow-up of our patient cohort.

Certain subsites, such as the nose and ear, warrant further consideration due to the potential for late effects including chondronecrosis. Low rates of toxicity was reported in a series of nasal SCCs treated predominantly with orthovoltage X-rays to a dose of 35Gy in 5 fractions for lesions <2 cm, 45Gy in 10 fractions for lesions 2–5 cm, and 50Gy in 20 fractions for lesions >5 cm or associated with bone or cartilage invasion [13]. Local relapse free survival was 90 % and 95 % at 2 and 5 year respectively. Similarly, Caccialanza et al. also showed low rates of radionecrosis with kilovoltage radiotherapy for skin cancers overlying the nasal cartilage [14]. Our series contains a substantial proportion of cancers treated in these location with 30 patients who had cancer of the nasal location and 18 patients with cancers of the ear. These were all treated with either electron or MV photon techniques, with low rates of acute and late toxicity. There were no reported chondronecrosis noted in follow up.

There is a growing evidence base supporting the efficacy of hypofractionated regimens. A large retrospective study of two fractionation schedules (54Gy in 18 fractions and 44Gy in 10 fractions) treated with electron beam technique found both schedules to be effective, with 3-year local recurrence free rates of 97.5 % and 96.1 %, with similar control rates for BCC and SCC [15]. The vast majority treated were located on the face (59.4 %) or elsewhere on the head (22.4 %). Silva et al. retrospectively analyzed the PMH experience for treatment of pinna SCC and BCCs with 313 patients and demonstrated a significant relationship between low BED and local control rate [16]. However, other studies have not been able to demonstrate a significant difference in outcome between dose fractionation schedules, despite not insignificant differences in BED [17]. A systematic review by Gunaratne et al., 2018, including 12,337 lesions treated with hypofractionated regimens across 40 publications, did not find any clear dose-response relationship [9].

Our patient cohort was elderly with a median age of 68 years. Over 20 % of the cohort was either immunosuppressed from a haematological malignancy or from treatment for another condition. The fractionation schedule was prescribed taking into consideration patient, tumour, and treatment factors. For patient factors, their co-morbidities and logistics in attending daily treatment were of great consideration in prescribing this fractionation schedule. Other significant considerations include field size/treatment volume. Several studies have reported that larger field size (>5cm2) and increasing dose per fraction correlated with incidence of radionecrosis [16,18]. In the study by Silva et al. reduced risk of necrosis and ulceration was shown when using fraction size <4Gy when treating skin cancers of the pinna, particularly when larger field sizes (>5 cm) were used [16]. Treatment volume data was not collected for this study, but our practice is to typically avoid hypofractionation regimens in the adjuvant setting following extensive surgery or with node positive disease, with patient factors permitting this approach. The 5-year OS was 69.9 %, with 16 of 21 deaths due to co-morbidities, reflecting that a significant proportion of these patients had comorbidities that likely factored into their radiotherapy decision.

A survey of radiotherapy practice in UK revealed a wide range of daily fractionation schedules, from 18 to 20Gy in 1 fraction to 55Gy in 20 fractions, with significant potential differences in radiobiological effect [19]. In summarizing their results, the authors suggested that publications of local outcomes by each institution would be beneficial in achieving a more consistent approach. Current NCCN guidelines offer a wide range of dose fractionation schedules for the treatment of skin cancers [20]. The economic healthcare burden associated with an ever-increasing older population is an important consideration when treatment guidelines are formed. The COVID-19 pandemic had a profound impact on treatment decisions globally. There is a strong push to select hypofractionated schedules in many tumour sites, where it is felt safe to do so [6,21]. The UK Royal College of Radiologist now recommend reducing the number of fractions for NMSC, for example using 50Gy in 15–20 fractions, reserving 60Gy in 30 fractions to treatments encompassing large area or in area of poor radiation tolerance [22]. However, particularly in the curative setting, it is imperative that sufficient evidence is available to support a chosen hypofractionated regimen, so as to not result in detriment to the patient.

We acknowledge there are limitations to this study. Due to the retrospective nature, the study is at risk of selection and recall bias. RT-related toxicities were collected retrospectively from review of medical records and discussion with the treating physician. Follow up duration and variable follow up schedule may not be sufficient to capture all late radiation toxicity.

5. Conclusion

Our study represents the largest series to report on a moderately hypofractionated RT regimen in the adjuvant setting for cutaneous SCCs and BCCs of the head and neck. Excellent local control rates were achieved with low rates of significant treatment-related non-skin toxicities. The 50Gy in 20# schedule can be considered an alternative option to conventionally fractionated regimens in well selected patients.

CRediT authorship contribution statement

Marcus Hu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Howard Liu:** Writing – review & editing, Formal analysis, Conceptualization. **Anne Bernard:** Formal analysis. **Michael Efendy:** Data curation. **Sandro V. Porceddu:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oor.2025.100732.

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