Radiation Oncology

BRIEF REPORT

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Hypofractionated versus standard fractionation radiotherapy for merkel cell carcinoma

Lorein Gonzalez[1], Muni Rubens[1], Sreenija Yarlagadda[1], Guilherme Rabinowits[1] and Noah S. Kalman[1*]

Abstract

Purpose/Objective(s) Merkel cell carcinoma (MCC) radiation treatment has historically consisted of standard 1.8–2 Gy fractions treated daily over 4–6 weeks. Hypofractionated treatment regimens have demonstrated tumor control and toxicity equivalence to standard fractionation regimens for common cutaneous malignancies such as basal cell and squamous cell carcinomas. Herein we report the outcomes of hypofractionated versus standard fractionation radiotherapy for MCC at our institution.

Materials/Methods The study involved a retrospective review of MCC patients treated with radiotherapy. Treatment characteristics and patient outcomes, including acute toxicities, disease recurrence and survival data were collected. The cumulative incidence of local and distant failures was estimated, with death as a competing risk.

Results A total of 29 treatment courses for 24 patients were included, of which 13 involved standard fractionation with curative intent, 10 involved hypofractionated radiotherapy with curative intent, and 6 involved single fraction (8 Gy) palliative radiation. Half the patients were treated to a head/neck site. A subset of patients treated adjuvantly with curative intent included 8 standard fractionation and 8 hypofractionated radiotherapy patients. No statistically significant differences in local and/or distant failure or overall survival was observed between the patient groups.

Conclusion Hypofractionated radiotherapy for MCC was associated with similar treatment outcomes relative to standard fractionation. In our limited patient sample, hypofractionated radiation treatment achieved similar results with similar toxicity and fewer treatments. Further analysis of a larger patient population with longer follow up is needed to confirm treatment tolerability and efficacy.

Keywords Merkel cell carcinoma, Hypofractionation, Radiation Therapy

*Correspondence:
Noah S. Kalman
noahk@baptisthealth.net
[1]Miami Cancer Institute, Baptist Health South Florida, 8900 N Kendall Dr, Miami, FL 33176, USA

Introduction

Merkel cell carcinoma (MCC) is a radiosensitive skin cancer. Local treatment typically consists of surgical excision and/or radiation therapy (RT). Historically, radiation treatment for MCC has involved standard 1.8–2 Gy fractions treated daily over 4–6 weeks for a cumulative dose ranging between 45 and 60 Gy [1]. For many malignancies, radiation treatment with daily doses > 2 Gy has increased in prevalence in order to reduce treatment times and increase patient convenience. The equivalence of such hypofractionated treatment regimens to standard fractionation regimens for tumor control and toxicity has been shown for common cutaneous malignancies such as basal cell and squamous cell carcinomas [2]. Similarly, there has been some suggestion of increased efficacy with hypofractionated radiation regimens over those using standard fractionation for melanoma due to favorable tumor radiobiology [3]. Recent publications have shown efficacy of hypofractionated radiotherapy for MCCs when treating with palliative and definitive intent [4, 5]. We made a change at our institution to hypofractionate the primary tumor site based on these reports. Herein we report the outcomes of hypofractionated versus standard fractionation radiotherapy for MCC at our institution.

Materials/methods

Data acquisition

Following institutional review board (IRB) approval, we conducted a retrospective review of 24 patient cases encompassing 29 treatment courses for patients with MCC of multiple body parts, including H&N, lower extremity, upper extremity, and trunk treated in the initial or recurrent setting. From this cohort, 8 received post-operative RT at 2 Gy per fraction, 8 received post-operative RT at 4 Gy per fraction (adjuvant nodal radiation received standard fractionation radiation if indicated), 5 received RT at 2 Gy per fraction and 2 received RT at 4 Gy per fraction (no nodal radiation received for hypofractionated patients) in the definitive setting, and 6 received 8 Gy SFRT in the palliative setting. Some overlap was observed in patients receiving RT in a definitive setting, which were later treated for recurrences. Patients' respective treatment details and outcomes were analyzed until the most recent follow-up. Pertinent patient characteristics such as age, gender, performance status, prior surgical and systemic therapy history, and tumor-related characteristics, including histology, location, stage, and nodal status, were recorded. In addition, treatment parameters such as target and RT field size, patient outcomes, namely, Radiotherapy Oncology Group (RTOG) acute toxicities, as well as recurrence and survival results, were collected. RT was delivered using one of 3 modalities: 3D photons, electrons, and protons.

Patient follow-up

The toxicity and cumulative incidence of local and distant failures were estimated, with death as a competing risk. Time to failure, either local or distant, was calculated from the date of RT simulation. Local failures were defined by local or regional tumor growth within treatment field or nodal marginal failures adjacent to the treatment field. Distant failures were defined when a malignancy was identified beyond the regional nodal drainage sites. Upon treatment completion, patients entered on surveillance, consisting of follow-up visits including physical examination and body imaging, approximately two to three months post-treatment completion and prior to each clinic visit per investigator's discretion. The first 12 months post-treatment follow up clinic visits were every three months, after which patients were seen every three to six months.

Statistical analysis

Patient's demographic and clinical characteristics were described using descriptive statistics such as frequencies and percentage for categorical variables and median and range for continuous variable. Patient characteristics were compared between patient all groups and also between adjuvant 2 Gy/fx and adjuvant 4 Gy/fx groups using Chi square or Fishers exact test for categorical variables and Mann-Whitney U or Kruskal-Wallis test for continuous variables. Time to event was also compared between patient groups. Kaplan Meier estimates were used to compare time to event analysis using log rank test. One year survival rates were also calculated using Kaplan Meier estimates. All statistical analysis were done using SAS version 9.4 (ASA Inc, Cary, NC). Statistical significant was set at $p < 0.05$.

Results

Twenty-nine treatment courses for 24 patients diagnosed with MCC treated from April 2018 to May 2023 were identified that met study criteria. Treatment details are provided in Table 1. The primary tumor site was located in the head and neck in 15 treatment courses (51.7%). From this cohort, 13 involved standard fractionation (2 Gy/day × 25–30 fractions) with curative intent, 10 involved hypofractionated radiotherapy (4 Gy/day × 10 fractions) with curative intent, and 6 involved single fraction (8 Gy) palliative radiation. Nodal basin radiation occurred in 12 (92.3%), 2 (20%), and 0 (0%) of standard fractionation, hypofractionation, and palliative treatment courses. Of the 24 patients, 15 (62.5%) were male and 9 (37.5%) were female. The patient cohort had a median age of 79 years, ranging from 51 to 93 years. Three patients received RT in the definitive setting and were later treated for recurrence in the palliative setting (1 patient also received a second curative intent treatment

Table 1 Treatment parameters and patient characteristics for all treatment groups

	Stratification				
	Palliative (*N* = 6)	**Post-op and Def 2 Gy/fx (*N* = 13)**	**Post-op and Def 4 Gy/fx (*N* = 10)**	**Total (*N* = 29)**	***P*-value**
Area, cm^2					0.870[1]
N	4	8	10	22	
Mean (SD)	306.3 (464.09)	94.8 (47.54)	97.1 (30.60)	134.3 (197.00)	
Median	102.5	76.6	92.1	92.1	
Range	20.3, 1000.0	42.3, 183.8	52.0, 141.8	20.3, 1000.0	
RT Total Dose, Gy					< .001[1]
N	6	13	10	29	
Mean (SD)	8.0 (0.00)	55.9 (4.27)	36.4 (10.06)	39.3 (19.53)	
Median	8.0	56.0	40.0	40.0	
Range	8.0, 8.0	50.0, 60.0	16.0, 48.0	8.0, 60.0	
RT Total Fractions, fx					< .001[1]
N	6	13	10	29	
Mean (SD)	1.0 (0.00)	28.4 (1.76)	9.1 (2.51)	16.1 (11.82)	
Median	1.0	28.0	10.0	10.0	
Range	1.0, 1.0	25.0, 30.0	4.0, 12.0	1.0, 30.0	
RT Type, n (%)					< .001[2]
3D	3 (50.0%)	0 (0.0%)	0 (0.0%)	3 (10.3%)	
Electrons + VMAT	3 (50.0%)	4 (30.8%)	10 (100.0%)	17 (58.6%)	
Protons	0 (0.0%)	6 (46.2%)	0 (0.0%)	6 (20.7%)	
VMAT	0 (0.0%)	3 (23.1%)	0 (0.0%)	3 (10.3%)	
Location Category, n (%)					0.606[2]
H&N	3 (50.0%)	8 (61.5%)	4 (40.0%)	15 (51.7%)	
Lower Extremity	0 (0.0%)	1 (7.7%)	2 (20.0%)	3 (10.3%)	
Trunk	2 (33.3%)	1 (7.7%)	1 (10.0%)	4 (13.8%)	
Upper Extremity	1 (16.7%)	3 (23.1%)	3 (30.0%)	7 (24.1%)	
Primary or recurrent, n (%)					0.023[2]
Primary	2 (33.3%)	11 (84.6%)	9 (90.0%)	22 (75.9%)	
Recurrent	4 (66.7%)	2 (15.4%)	1 (10.0%)	7 (24.1%)	
Nodal Status, n (%)					< .001[2]
Negative	0 (0.0%)	2 (15.4%)	6 (60.0%)	8 (27.6%)	
Positive	1 (16.7%)	11 (84.6%)	1 (10.0%)	13 (44.8%)	
Unknown (Nx)	5 (83.3%)	0 (0.0%)	3 (30.0%)	8 (27.6%)	
ECOG, n (%)					0.254[2]
0	0 (0.0%)	6 (46.2%)	4 (40.0%)	10 (34.5%)	
1	3 (50.0%)	6 (46.2%)	2 (20.0%)	11 (37.9%)	
2	2 (33.3%)	1 (7.7%)	3 (30.0%)	6 (20.7%)	
3	1 (16.7%)	0 (0.0%)	1 (10.0%)	2 (6.9%)	
Acute Dermatits Grade, n (%)					0.006[2]
0	5 (83.3%)	0 (0.0%)	3 (30.0%)	8 (27.6%)	
1	1 (16.7%)	4 (30.8%)	4 (40.0%)	9 (31.0%)	
2	0 (0.0%)	5 (38.5%)	3 (30.0%)	8 (27.6%)	
3	0 (0.0%)	4 (30.8%)	0 (0.0%)	4 (13.8%)	
Other Acute Toxicity G2+, n (%)					0.190[2]
(G2) dysgeusia	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (3.4%)	
(G2) fatigue	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.4%)	
(G2) skin ulceration	2 (33.3%)	0 (0.0%)	0 (0.0%)	2 (6.9%)	
Edema limbs (G3), (G2) esophagitis	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (3.4%)	
G2 xerostomia, G2 dysgeusia	0 (0.0%)	0 (0.0%)	1 (10.0%)	1 (3.4%)	
G3 skin ulceration, G2 pain	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	
dental caries	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (3.4%)	
fatigue (2)	0 (0.0%)	1 (7.7%)	0 (0.0%)	1 (3.4%)	

Table 1 (continued)

	Stratification				
	Palliative (*N* = 6)	**Post-op and Def 2 Gy/fx (*N* = 13)**	**Post-op and Def 4 Gy/fx (*N* = 10)**	**Total (*N* = 29)**	***P*-value**
n/a	3 (50.0%)	9 (69.2%)	8 (80.0%)	20 (69.0%)	
Time duration of RT, days					< .001[1]
N	6	13	9	28	
Mean (SD)	0.0 (0.00)	39.2 (3.37)	41.4 (44.06)	31.5 (29.37)	
Median	0.0	39.0	25.0	35.0	
Range	0.0, 0.0	34.0, 45.0	14.0, 156.0	0.0, 156.0	
Time sim to end of RT, days					< .001[1]
N	6	13	9	28	
Mean (SD)	6.5 (4.59)	55.5 (6.28)	53.9 (44.31)	44.5 (31.80)	
Median	7.0	54.0	39.0	50.0	
Range	0.0, 13.0	46.0, 70.0	24.0, 167.0	0.0, 167.0	
Time surgery to sim, days					0.029[1]
N	3	11	10	24	
Mean (SD)	662.3 (383.50)	128.0 (234.51)	30.6 (6.72)	154.2 (278.15)	
Median	662.0	32.0	29.5	32.5	
Range	279.0, 1046.0	18.0, 811.0	21.0, 41.0	18.0, 1046.0	

[1]Kruskal-Wallis *p*-value; [2]Chi-Square *p*-value;

for a nodal recurrence, and 1 patient received 2 palliative treatment courses).

A subset of treatment courses involved adjuvant therapy after primary surgery with curative intent included 8 standard fractionation and 8 hypofractionated radiotherapy patients. Median treatment time was 39 days versus 25 days for standard fractionation versus hypofractionated radiotherapy patients, respectively (Table 2).

At a median 10-month follow up, no locoregional failures occurred in the standard fractionation group, and 1 regional failure occurred in an untreated nodal basin in the hypofractionated radiotherapy group. For these patients, initial treatment consisted of wide local excision and SLNB or neck dissection followed by adjuvant RT. No patients had a history of prior radiation therapy to sites treated, while 3 had a history of prior systemic therapy.

At a median follow-up time of 12 months, the survival probability for patients who received adjuvant RT in standard fractionation was 100% and 83.3% (95% CI, 53.5-100.0%) for individuals in the adjuvant hypofractionated group (Fig. 1). For patients treated definitively and postoperatively, the 12-month survival probability at standard fractionation was 90.9% (95% CI, 73.9%-100.0) and 71.4% (95% CI, 38.0-100.0%) hypofractionated; for palliative radiation therapy, a 12-month survival probability of 41.7% (95% CI, 0.0-100.0%) was observed (Fig. 2). There were 5 patient deaths noted during the follow-up period. No statistically significant differences in locoregional and distant failure or overall survival were observed between the adjuvant radiotherapy groups treated to the primary site with standard fractionation versus hypofractionated schedules.

Acute dermatitis toxicity was minimal with hypofractionated treatment, with 0% of hypofractionated patients experiencing grade 3+toxicity compared to 30.8% of patients receiving standard fractionation (Table 1). Skin ulceration toxicity was also minimal with hypofractionated and standard fractionation patients, with 0% of patients experiencing grade 2+toxicity in both cohorts, compared to 33.3% (2 patients) of patients receiving palliative radiation (Table 1). No RTOG grade 4+acute toxicity was reported.

Discussion

In this retrospective study, we compared treatment outcomes of different fractionation regimens for MCC patients, specifically examining a uniform moderately hypofractionated regimen for adjuvant radiotherapy for this patient population. The early results indicate that hypofractionated regimens had comparable disease control and toxicity compared to standard fractionation regimens. These outcomes are consistent with previous studies which showed comparable disease control with hypofractionated regimens [4]. For the patients receiving single fraction palliative RT, our outcomes mirror other reports showing acceptable symptom palliation [6].

Excluding palliative intent patients, no statistically significant difference in locoregional control between hypofractionation versus standard fractionation was observed in the current report. Two locoregional failures occurred in patients receiving hypofractionated RT with curative intent. In both cases, the recurrence occurred outside the treatment field. That no local failures occurred among any standard or hypofractionated treatment course confirms the radiosensitivity of MCC. Regarding the

Table 2 Treatment parameters and patient characteristics for adjuvant standard and hypofractionated groups

	Stratification			
	Post-op 2 Gy/fx (*N* = 8)	**Post-op 4 Gy/fx (*N* = 8)**	**Total (*N* = 16)**	***P*-value**
Area, cm^2				0.332[1]
N	6	8	14	
Mean (SD)	101.4 (50.24)	107.5 (24.26)	104.9 (36.02)	
Median	76.6	98.1	92.1	
Range	64.0, 183.8	81.3, 141.8	64.0, 183.8	
RT Total Dose, Gy				< .001[1]
N	8	8	16	
Mean (SD)	53.6 (3.87)	38.0 (9.32)	45.8 (10.60)	
Median	53.2	40.0	49.0	
Range	50.0, 60.0	16.0, 48.0	16.0, 60.0	
RT Total Fractions, fx				< .001[1]
N	8	8	16	
Mean (SD)	27.5 (1.69)	9.5 (2.33)	18.5 (9.50)	
Median	28.0	10.0	18.5	
Range	25.0, 30.0	4.0, 12.0	4.0, 30.0	
RT Type, n (%)				0.121[2]
Electrons + VMAT	4 (50.0%)	8 (100.0%)	12 (75.0%)	
Protons	3 (37.5%)	0 (0.0%)	3 (18.8%)	
VMAT	1 (12.5%)	0 (0.0%)	1 (6.3%)	
Location Category, n (%)				0.454[2]
H&N	5 (62.5%)	2 (25.0%)	7 (43.8%)	
Lower Extremity	1 (12.5%)	2 (25.0%)	3 (18.8%)	
Trunk	1 (12.5%)	1 (12.5%)	2 (12.5%)	
Upper Extremity	1 (12.5%)	3 (37.5%)	4 (25.0%)	
Nodal Status, n (%)				0.037[2]
Negative	2 (25.0%)	6 (75.0%)	8 (50.0%)	
Positive	6 (75.0%)	1 (12.5%)	7 (43.8%)	
Unknown (Nx)	0 (0.0%)	1 (12.5%)	1 (6.3%)	
ECOG, n (%)				0.766[2]
0	4 (50.0%)	4 (50.0%)	8 (50.0%)	
1	3 (37.5%)	2 (25.0%)	5 (31.3%)	
2	1 (12.5%)	2 (25.0%)	3 (18.8%)	
Acute Dermatits Grade, n (%)				0.319[2]
0	0 (0.0%)	2 (25.0%)	2 (12.5%)	
1	4 (50.0%)	3 (37.5%)	7 (43.8%)	
2	4 (50.0%)	3 (37.5%)	7 (43.8%)	
Other Acute Toxicity G2+, n (%)				0.368[2]
G2 xerostomia, G2 dysgeusia	0 (0.0%)	1 (12.5%)	1 (6.3%)	
dental caries	1 (12.5%)	0 (0.0%)	1 (6.3%)	
n/a	7 (87.5%)	7 (87.5%)	14 (87.5%)	
Time duration of RT, days				0.044[1]
N	8	8	16	
Mean (SD)	38.8 (4.10)	27.9 (9.49)	33.3 (9.02)	
Median	38.5	24.5	35.0	
Range	34.0, 45.0	21.0, 43.0	21.0, 45.0	
Time sim to end of RT, days				0.024[1]
N	8	8	16	
Mean (SD)	56.9 (7.14)	39.9 (13.20)	48.4 (13.50)	
Median	55.0	34.0	52.5	
Range	48.0, 70.0	28.0, 64.0	28.0, 70.0	
Time surgery to sim, days				0.713[1]

Table 2 (continued)

	Stratification			
	Post-op 2 Gy/fx (*N* = 8)	**Post-op 4 Gy/fx (*N* = 8)**	**Total (*N* = 16)**	***P*-value**
N	8	8	16	
Mean (SD)	32.1 (16.88)	29.6 (6.37)	30.9 (12.39)	
Median	29.0	29.5	29.0	
Range	18.0, 70.0	21.0, 39.0	18.0, 70.0	

[1]Kruskal-Wallis *p*-value; [2]Chi-Square *p*-value

appropriate hypofractionated dose for MCC, the 40 Gy in 10 fractions used in the current study has a higher biologically effective dose (BED) than most doses used in a previous study (30–35 Gy in 10 fractions or 45 Gy in 20 fractions), although one dose schedule used (50 Gy in 20 fractions) has a slightly higher BED based on an alpha/beta ratio of 10 (BED10) [4]. Overall, the dose used in this study appears suitable for further investigation. Further clarification of the alpha/beta ratio specific to MCC may allow for better tailoring of treatment doses.

Regarding toxicity, hypofractionated treatment was well tolerated. Patient treatment times were roughly 2 weeks shorter with hypofractionated courses. Of note, all patients that received adjuvant nodal radiation received standard fractionation radiation. Only the primary tumor site received hypofractionated RT given the extensive safety data for such treatment regimens [2]. The use of hypofractionated RT in our cohort was therefore limited to treatment of the primary site in which toxicity data exists. This report provides further support for the use of hypofractionated regimens in MCC.

A statistically significant reduction in overall survival (OS) was observed with hypofractionated patients. This is consistent with a previous report [4]; another study attributed lower OS with lower radiation doses, although differences in local recurrence was not evaluated as function of radiation dose [7]. Our findings suggest that patients undergoing hypofractionated therapy may have had additional comorbidities. It is possible that lower BED10 with hypofractioned regimens is a cause for worse survival, but the lack of local failures makes this explanation less likely.

Our study is limited by factors inherent in retrospective studies and the small sample size. More patients and longer follow up is important to confirm this study's findings. Nonetheless, the results of the current analysis support and build upon previous reports of hypofractionated RT for MCC.

Conclusion

Hypofractionated radiotherapy for MCC was associated with similar treatment outcomes relative to standard fractionation regimens in the curative intent setting. In our limited patient sample, hypofractionated radiation treatment achieved similar results with similar toxicity and fewer treatments. Further analysis of a larger patient population with longer follow up is needed to confirm treatment tolerability and efficacy.

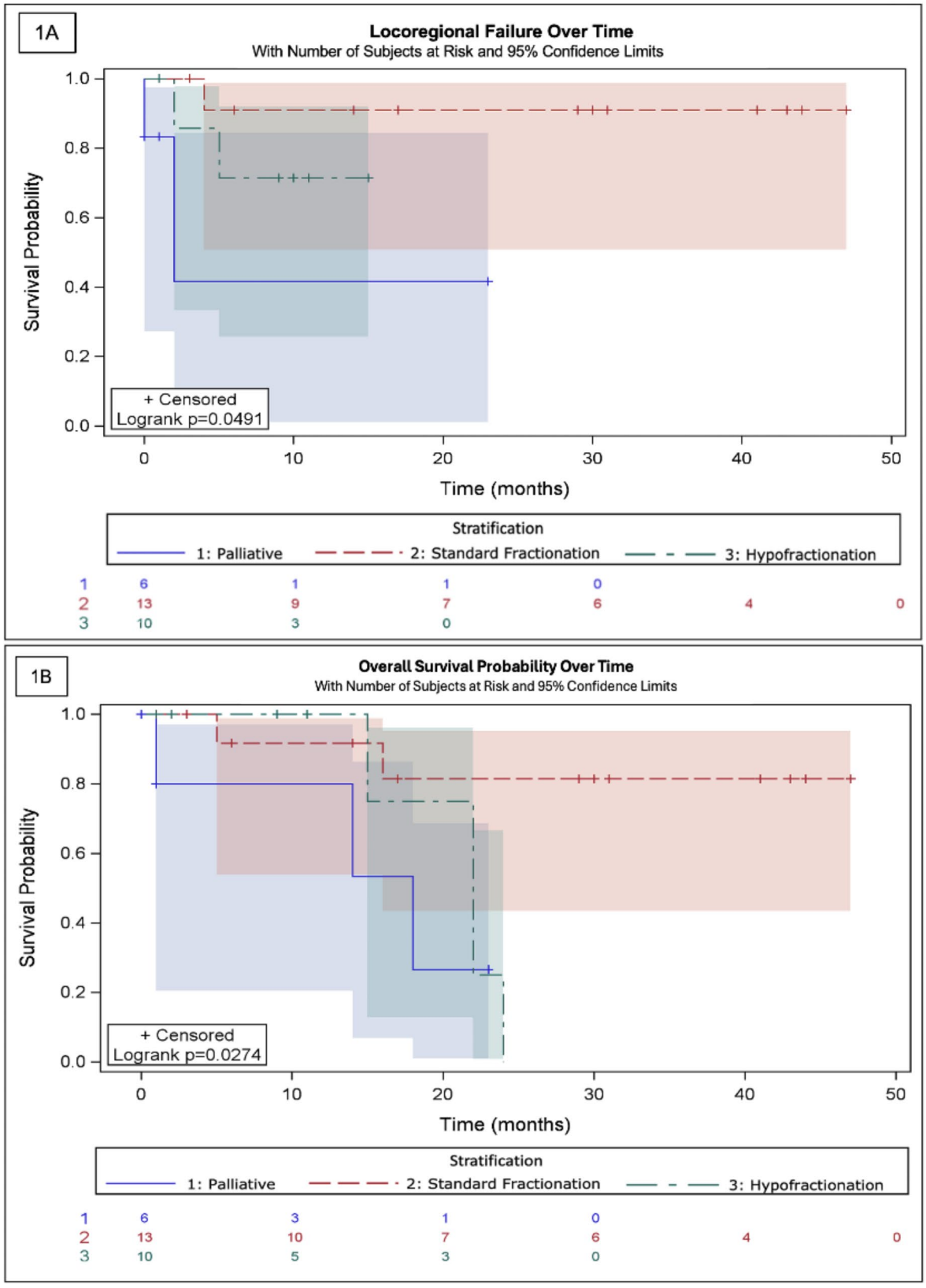

Fig. 1 Disease control outcomes for all treatment groups. 1a) Incidence of locoregional failure; 1b) Overall survival probability

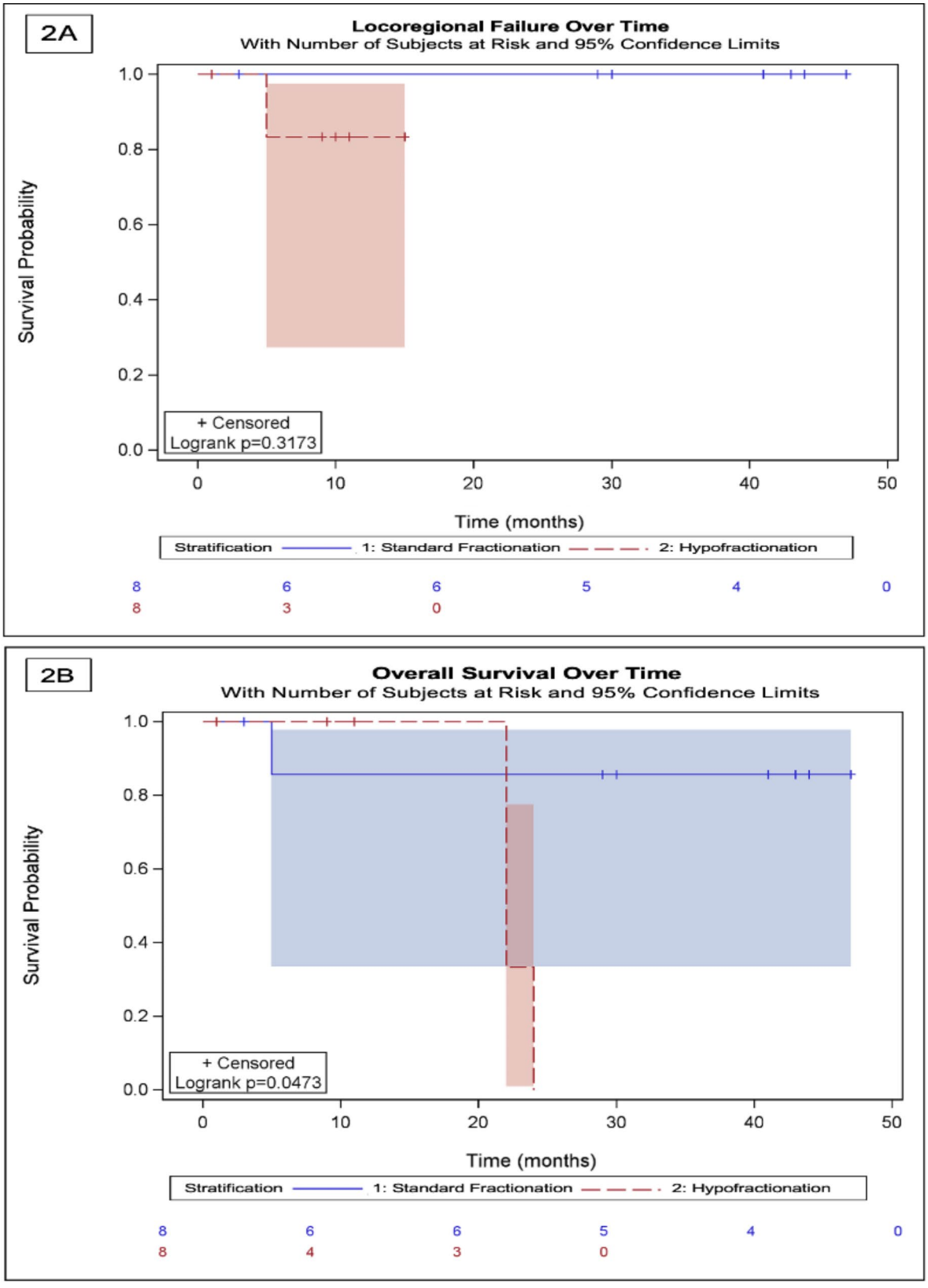

Fig. 2 Disease control outcomes for standard fractionation and hypofractionation groups. 2a) Incidence of locoregional failure; 2b) Overall survival probability

Abbreviations

MCC	merkel cell carcinoma
RT	radiation therapy
Gy	gray
IRB	institutional review board
H&N	head and neck
SFRT	single fraction radiation therapy
RTOG	Radiotherapy Oncology Group
SLNB	sentinel lymph node biopsy
OS	overall survival
BED10	biologically effective dose with alpha/beta ratio of 10

Author contributions
L.G. and N.S.K. wrote the main manuscript text and L.G. prepared the figures and tables. M.R. was responsible for the statistical analyses. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

IRB approval status
Reviewed and approved by MCI IRB; study #2023-RETRO-KAL-001.

Ethics approval and consent to participate
Not applicable (retrospective study).

Competing interests
The authors declare no competing interests.

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