



Importance of Margins, Radiotherapy, and Systemic Therapy in Mucosal Melanoma of the Head and Neck

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Abstract

Objectives: The ideal strategy in the treatment of mucosal melanoma of the head and neck (MMHN) remains unclear. Our objective was to evaluate the importance of surgical margins, radiotherapy, and systemic therapy in MMHN.

Study design: Retrospective Single Institutional Review.

Methods: Retrospective review of patients with MMHN treated at a tertiary care oncology center between 1999 and 2016.

Results: Seventy-six patients were included, 60 of whom were treated with curative intent. Negative or close margins compared with positive margins were associated with higher 3-year overall survival (OS) (62% vs. 29% vs. 13% $P = .012$), disease-free survival (33% vs. 29% vs. 4% $P = .003$), and distant control (48% vs. 29% vs. 22% $P = .039$). Cases with pre-/postoperative radiotherapy had a marginally higher locoregional control versus without (69% vs. 59%, $P = .117$). Immunotherapy for recurrent and/or metastatic disease was associated with an increase in 3-year OS (15% vs. 3% $P = .01$).

Conclusion: Achieving negative surgical margins is relevant in disease control. Despite small sample size, our data suggest that radiotherapy may enhance surgical outcomes. Immunotherapy has therapeutic benefit.

Introduction

Mucosal melanoma is a rare disease, accounting for approximately 1.4% of all melanomas^{1,2}. In the head and neck region, mucosal melanomas of the HN (MMHN) represent 10% of all melanomas (90% cutaneous melanomas) and have a dismal prognosis. Compared to cutaneous melanomas, which have a 5-year overall survival (OS) of 81% across all stages, the reported 5-year OS for mucosal melanomas is 25%³.

The rarity of MMHN precludes large prospective trials to evaluate the efficacy of various treatment modalities, and controversies remain about the optimal treatment strategy. Specifically, there is continued debate surrounding the value of surgical margins^{4,5} and adjuvant therapies^{6,7}.

The objective of this study was to report our experience with MMHN, focusing on the importance of surgical margins, role of RT, and immunotherapy in the overall treatment strategy.

Methods and Materials

Patients ≥ 18 years with MMHN were recruited between March 1999 and August 2016. Patient demographics, tumor location, stage, treatment intent, treatment modalities (surgery, RT, systemic therapies), surgical margin(s), and disease status were collected. Surgical margins were classified as negative, close, or positive. Margins were considered close when the tumor edge was <5 mm from the resection margin in any plane. Piecemeal resection was considered positive or close based on interpretation of pathology and surgical reports. Treatment decisions reviewed in the multidisciplinary tumor board. Post-op RT was indicated in patients with close or positive margins, in T4 tumors, and/or multifocal primary lesions. Post-op chemotherapy was indicated when positive margins were obtained. Immunotherapy was given in patients who had recurrences and/or developed metastasis after curative treatment.

Outcome endpoints included OS, disease-free survival (DFS), locoregional control (LRC), and distant control (DC). Patients were deemed palliative if they presented with distant disease at diagnosis, very advanced disease unamenable for curative local treatment, multiple comorbidities, and/or extremely poor performance status precluding curative treatment.

Results

- Seventy-six patients were included. Sixty (79%) patients were treated with curative intent, and 16 (21%) were deemed palliative.
- In the curative cohort, 53 (88%) patients had surgery: 42 (79%) transfacially, 10 (19%) endoscopically, and 1 (2%) via robotic surgery.
- Negative, close and positive margins were 43%, 14% and 43%. Neck dissection was performed in 33% patients. 15 patients were pN1. Occult nodal metastasis occurred in 14% of cN0 cases.
- RT was delivered in 47 patients with curative intent using 2 Gy per fraction. Definitive RT was given in seven patients: Five due to unresectable disease and two for functional considerations. RT regimens comprised 60 to 70 Gy in 30 to 35 fractions over 6 to 7 weeks (60–70 Gy/30–35f/6–7w) with elective dose of 50 to 56 Gy/30to 35f to the uninvolved neck.
- In the curative setting, 3-year DFS, LRC, and DC were 17%, 69%, and 33%, respectively. No significant differences were apparent in OS (35% vs. 14% $p=.183$), LRC (67% vs. 86% $p=.339$), and DC (33% vs. 0% $p=.170$) between surgery versus definitive RT, whereas DFS was superior in the surgical group (20% vs. 0% $p=.001$).
- Negative or close margins versus positive margins had improved 3-year OS 62% vs. 29% vs. 13% ($P = .012$), DFS 33%, 29%, and 4% ($P = .003$), and DC 48%, 29%, and 22% ($P = .039$), respectively (**Fig. 1**). Multivariable analysis confirmed the prognostic detriment of positive versus negative margins (**Table 2**).
- There was a trend towards higher 3-year LRC in patients with ($n=40$) versus without ($n=13$) post-op RT (69% [50–81] vs. 59% [15–80], $P = .117$) although OS was not significant ($P = .338$) (**Fig. 2**).
- In 13 patients who recurred after initial curative treatment, 3-year OS was higher for those received immunotherapy versus without (15% vs. 3%, $P = .01$) (**Fig. 3**). Patients treated with immunotherapy had the highest survival after disease recurrence with a small portion of patients surviving their disease (**Fig. 4**).

Fig 1. OS (A), DFS (B), DC (C), and LC (D) in patients treated surgically with curative intent stratified by margin status

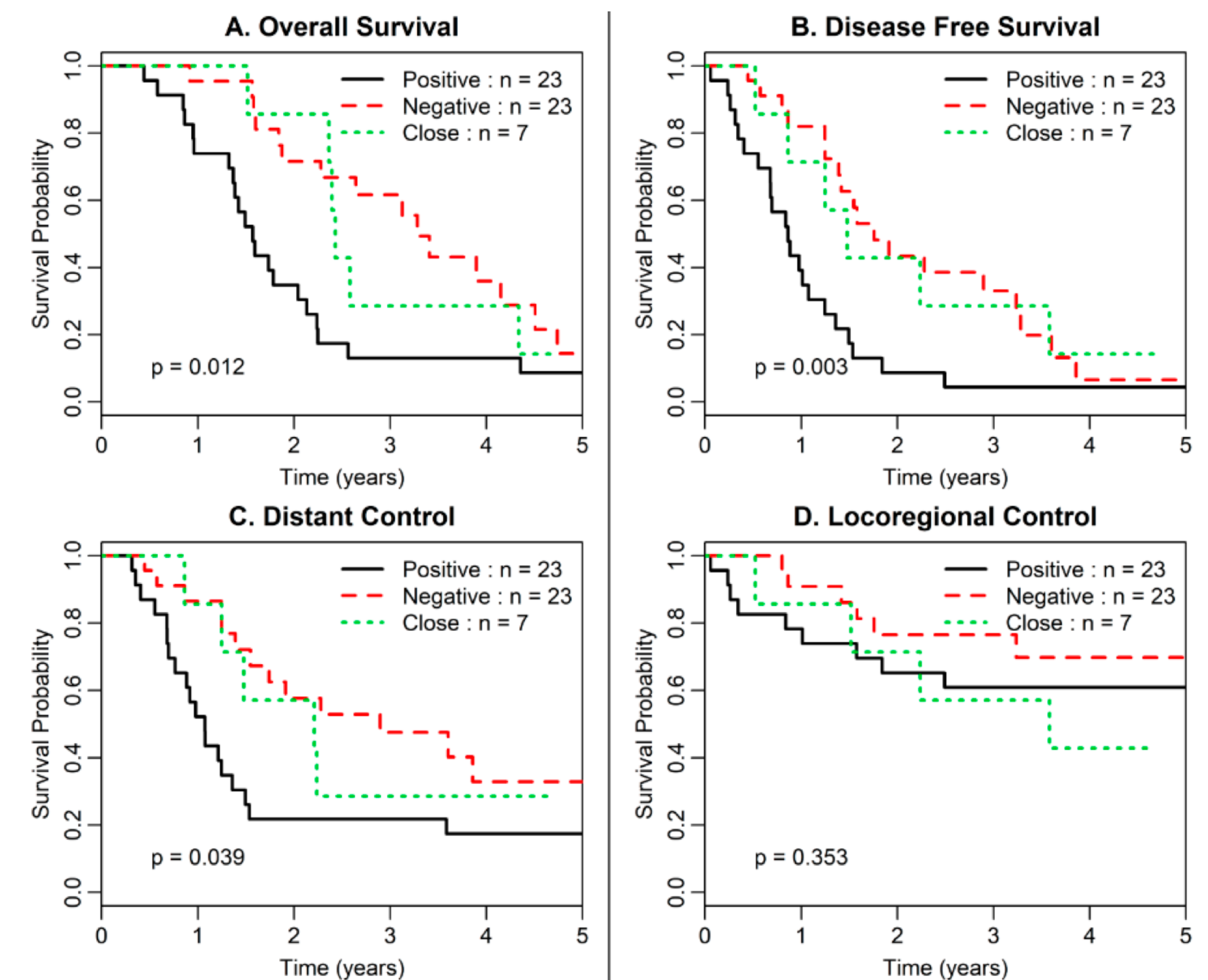
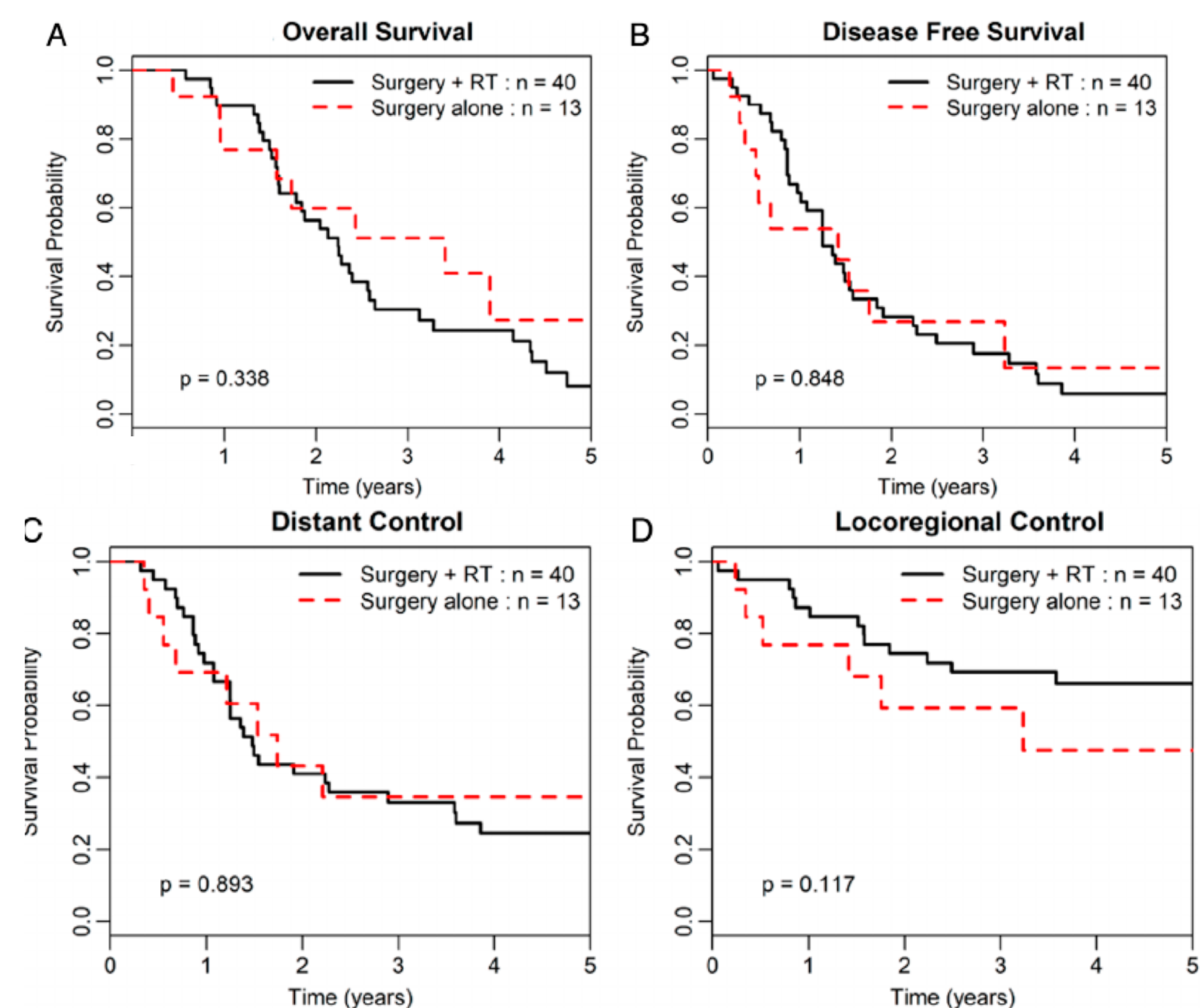


Table 2. Univariable and Multivariable Analysis of Outcomes by Resection Margin Status in Patients Treated Curatively.

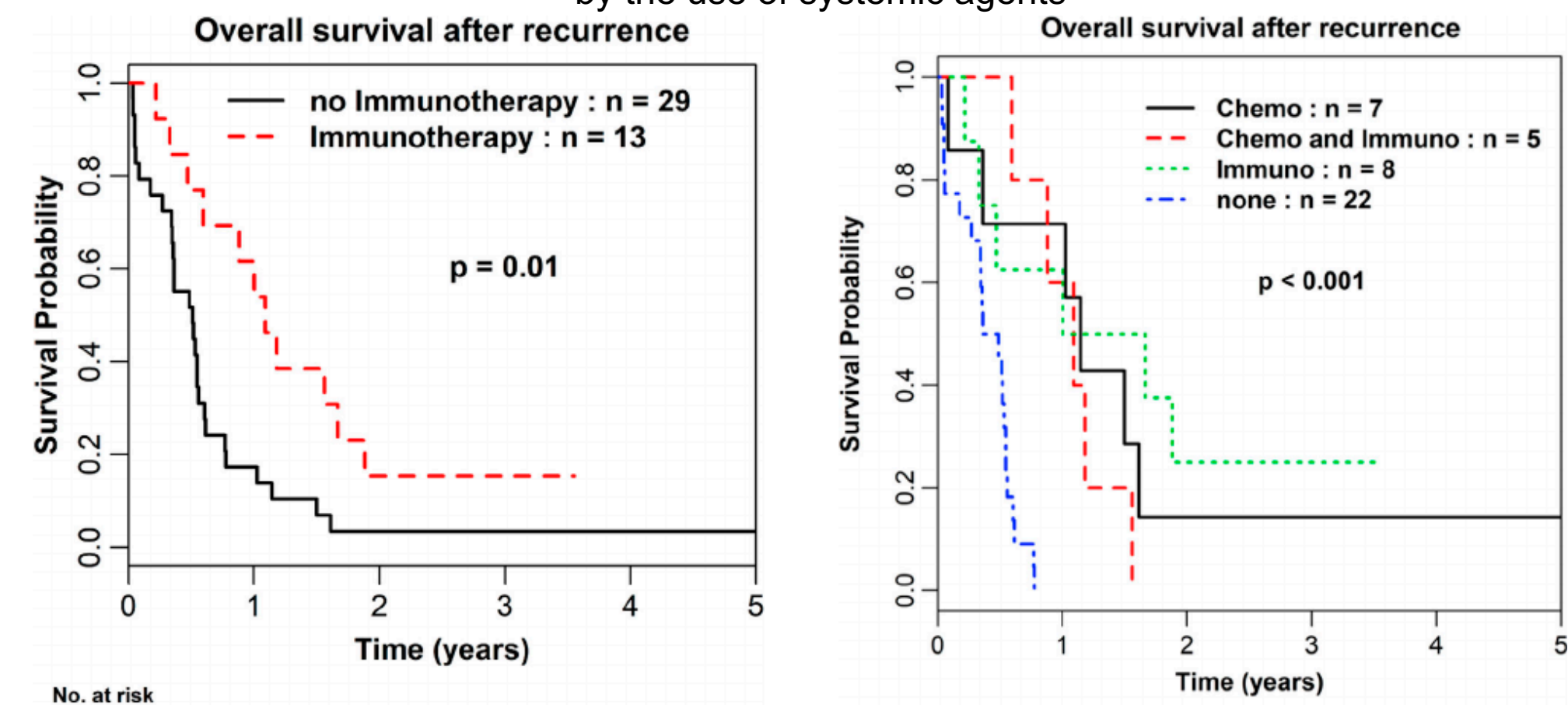
Comparison	Analysis	OS	DFS	DC	LRC
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Close vs Negative	Univariable	1.25 (0.49-3.22)	1.10 (0.44-2.78)	1.25 (0.51-3.06)	2.30 (0.72-7.27)
	p value	0.640	0.840	0.630	0.160
Positive vs Negative	Univariable	2.55 (1.32-4.92)	2.75 (1.46-5.18)	2.46 (1.20-2.07)	1.80 (0.66-4.90)
	p value	0.005	0.002	0.015	0.250
Close vs Negative	Multivariable	1.27 (0.49-3.28)	1.03 (0.40-2.64)	1.29 (0.53-3.12)	2.31 (0.70-7.64)
	p value	0.620	0.940	0.57	0.450
Positive vs Negative	Multivariable	2.47 (1.27-4.82)	2.96 (1.54-5.68)	2.54 (1.26-5.10)	1.81 (0.64-5.15)
	p value	0.008	0.001	0.009	0.260

* Multivariable analysis adjusted for age for overall survival and disease-free survival, and N-category for locoregional control and distant metastasis.

Fig 2. OS (A), DFS (B), DC (C), and LC (D) in patients treated surgically with curative intent with versus without radiotherapy



Figs 3 and 4. OS in patients treated surgically with curative intent who recurred with and without immunotherapy, and stratified by the use of systemic agents



Discussion and Conclusions

We consider that achieving negative surgical margins is relevant in managing MMHN, and provides evidence of the potential therapeutic benefit of immunotherapy in this disease. Albeit a small sample, our study suggests that RT may enhance surgical outcomes. The prognosis for this population is unsatisfactory regardless of local treatment; the major therapeutic challenge is eradicating DM where immunotherapy shows some promising results. Multi-institutional prospective collaborations are required to help elucidate the optimal management of this rare disease

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