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Recurrence Rates Over 20 Years in the Treatment of Malignant Melanoma: Immediate Versus Delayed Reconstruction

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Background: Wide local excision (WLE) with a safety margin is the standard of treatment for primary head and neck cutaneous malignant melanoma (HNCMM). Studies have demonstrated inconsistency in recurrence rates following immediate versus delayed reconstruction. The objectives of this study were to assess and compare recurrence rates after WLE of HNCMM followed by immediate or delayed reconstruction in determining recurrence-free survival estimates.
Methods: A consecutive, retrospective analysis of 451 patients undergoing WLE of primary HNCMM followed by reconstruction over a period of 20 years was performed. Patients were divided into 2 groups based on timing of reconstruction (immediate versus delayed). Univariate analyses were performed to assess distributions. Kaplan–Meier survival analysis and multivariate Cox proportional hazard analyses were performed to estimate recurrence-free survival.
Results: Tumor specimen positive margins were comparable between immediate and delayed reconstruction groups ($P = 0.129$). Univariate analysis demonstrated comparable local melanoma recurrence after immediate or delayed reconstruction (41.4% versus 53.3%; $P = 0.399$). After adjusting for prognostic factors, multivariate analysis also failed to demonstrate an association between reconstruction timing and local recurrence-free survival ($P = 0.167$).
Conclusions: In this long-term study, we were not able to demonstrate an association between reconstruction timing and local recurrence-free survival after excision WLE of HNCMM, rendering immediate reconstruction a reliable approach. In addition, the presence of ulceration and a positive sentinel lymph node were positively associated with the risk of recurrence. *(Plast Reconstr Surg Glob Open 2017;5:e1378; doi: 10.1097/GOX.0000000000001378; Published online 12 July 2017.)*

INTRODUCTION

Melanoma is the most fatal form of skin cancer, and its incidence has steadily increased over the past decades (1–9). Since the early 1970s, the incidence of melanoma in the United States has increased from 6.8 to 20.1 per 100,000 people.[1] Cutaneous malignant melanoma comprises only 4–11% of all skin cancers but is the major cause of skin cancer–related deaths (75%); approximately 20% of these tumors are found in the head and neck.[2,3] Currently, the standard of treatment for primary head and neck cutaneous malignant melanoma (HNCMM) includes wide local excision (WLE) with a safety margin of uninvolved adjacent tissue.

WLE and subsequent reconstruction can be either immediate, without prior histopathological review of margins, or delayed, after histopathological analysis of the specimen. Although immediate reconstruction following WLE remains controversial, previous studies have shown that it can be performed safely and reliably.[3–5] Furthermore, single-stage reconstruction has the advantage of increased patient convenience and potentially lower health-care costs. However, concerns for local recurrence have made delayed reconstruction the mainstay of defect reconstruc-

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tion in head and neck melanoma in certain centers.[2,3] The best oncologic result of low positive margin rates and most optimal aesthetic outcome can be attained when surgical oncologists and plastic surgeons work closely together in the planning and execution of WLE and reconstruction.[4]

The objectives of this study were (1) to compare the frequency of positive tumor margins after WLE of HNCMM followed by immediate or delayed reconstruction, (2) to assess and compare recurrence rates, (3) to determine recurrence-free survival estimates, and (4) to assess if timing of reconstruction (immediate versus delayed) was associated with overall local recurrence-free survival.

METHODS

Study Design

We performed a retrospective analysis of 451 consecutive patients undergoing WLE of solitary, primary HNCMM followed by reconstruction over a period of 20 years (1994–2014) at the Beth Israel Deaconess Medical Center. This study was approved by the institutional review board at our medical center. Data collected included patient demographics, comorbidities, melanoma type and anatomic location, size (recorded as the maximum diameter), melanoma thickness as defined by Breslow,[6] primary tumor, nodal involvement, metastasis (TNM) stage,[7] Clark level, presence of ulceration, reconstruction timing, reconstruction type, margin status after WLE, lymph node involvement, reexcision rates following reconstruction of WLE, and recurrence rates.

WLE was performed according to recommended guidelines dependent on tumor characteristics: 1 cm for T1 tumors (≤ 1 mm in thickness), and 2 cm for T2 (1.01–2 mm), T3 (2–4 mm), and T4 (4 mm) tumors.[8–14] Local recurrences were defined as tumor regrowth within 2 cm of the surgical scar following definitive excision of a primary melanoma with appropriate surgical margins.[12] Recurrences that were greater than 2 cm from the primary lesion but not beyond the regional nodal basin were termed in-transit metastases.[15] Regional recurrence was defined as recurrence within the head and neck region (within the first and second echelon lymph nodes) and nodal recurrence was defined as recurrence involving lymph nodes for primary melanoma with lymph node involvement.[15] Immediate reconstruction was defined as any type of wound closure at the time of primary excision, without prior knowledge of histopathological tumor margins. In contrast, delayed reconstruction was described as wound closure after acknowledgment of tumor specimen margin status. Excision and reconstruction were performed by 2 experienced craniofacial surgeons (S.L. and R.F.), as well as the decision for reconstruction timing dependent on concerns for a positive tumor margin after WLE. Exclusion criteria included Mohs surgery or unspecified timing of reconstruction and metastatic disease.

Statistical Analysis

Statistical analyses were performed using SPSS Software version 22.0 (SPSS Inc., Chicago, Ill.). Chi-square tests, Fisher's exact tests, and Student *t* tests were performed to compare categorical and continuous variables. Kaplan–Meier survival analysis and the Log-rank test were applied in the comparison of recurrence rates between immediate and delayed groups. Data on patients lost to follow-up for geographical reasons have been included for survival analysis but censored. A multivariate COX proportional hazard model based on melanoma prognostic factors[16,17] was configured to adjust for potential confounders and to obtain hazard ratios. All calculated *P* values were 2-tailed and a *P* value of < 0.05 was deemed statistically significant. Missing data were considered "missing completely at random," which allowed for complete case analysis. As post hoc power analysis for survival curves are considered an inappropriate approach in this specific setting, associated 95% confidence intervals (CIs) are reported.[18,19] Each covariate was specifically tested separately and globally for the assumption of proportional hazards.

RESULTS

Demographics

A total of 451 consecutive patients with a history of primary HNCMM between 1994 and 2014 were included in this study. Of these, 207 patients were included for data analysis with complete follow-up data. Overall mean age at the time of WLE and follow-up time were 60.0 ± 15.9 years and 1,470 ± 1,160 days, respectively. The male:female ratio was increased in both groups; however, a similar distribution was observed ($P = 0.242$). Furthermore, there were no significant differences in comorbidities therapy between groups (Table 1).

Melanoma Characteristics

In our population, the most prevalent subtypes of HNCMM were invasive lentigo maligna melanoma (24.6%), superficial spreading melanoma (21.7%), and nodular melanoma (15.5%). Subgroup analysis did not detect a significant difference in distribution of HNCMM subtypes among groups ($P = 0.086$; Fig. 1).

Melanoma size (immediate: 13.1 mm versus delayed: 12.7 mm; $P = 0.856$) and Breslow depth (immediate: 3.2 mm versus delayed: 2.5 mm; $P = 0.355$) were comparable in both groups. Furthermore, tumor stage ($P = 0.313$) and Clark level ($P = 0.107$) were also similar. Univariate analyses demonstrated melanoma with ulceration were more likely to have undergone subsequent immediate reconstruction compared with delayed (28.4% versus 14.1%; $P = 0.026$; Table 1). A higher overall anatomical prevalence of melanoma on the cheek (27.1%) was noted, followed by the scalp (23.7%) and ear/peri-auricular region (15.5%). When anatomic distribution was analyzed per group, immediate reconstruction was more prevalent on the scalp (29.4%) in comparison with a delayed procedure, which was more prevalent on the cheek (42.2%; Fig. 2).

Margins Status and Type of Reconstruction

On univariate analysis, we found no significant difference in positive tumor margins requiring reexcision between immediate and delayed reconstruction cases (16.1% versus 25.0%; $P = 0.129$). Reexcision of residual

Table 1. Patient Demographics and Tumor Characteristics

Characteristics	Total (%)	Immediate (%)	Delayed (%)	Unadjusted *P*
Number of patients	207	143	64	
Mean follow-up (mo)	48.2±38.2	47.8±41.0	49.2±31.2	0.807*
Mean delay time (d)	N/A	N/A	8.9±5.4, range, 3–31	N/A
Sex				0.242†
Male	138	99	39	
Female	69	44	25	
Age at operation (y)	60.0±16.0	58.9±15.2	62.5±17.5	0.126*
BMI (kg/m^2)	27.9±5.0	27.4±5.0	28.5±5.1	0.249*
Diabetes	17 (8.2)	12 (8.4)	5 (7.8)	0.888†
Hypertension	86 (41.5)	56 (39.2)	30 (46.9)	0.298†
Smoking	24 (11.6)	17 (11.9)	7 (10.9)	0.843†
Melanoma diameter (mm)	13.0±13.0	13.1±14.4	12.7±10.0	0.856*
Breslow thickness (mm)	3.0±4.9	3.2±5.6	2.5±2.6	0.355*
Tumor stage				0.313†
Tis	11 (5.6)	5 (3.7)	6 (9.7)	
T1	84 (42.4)	59 (43.4)	25 (40.3)	
T2	56 (28.3)	38 (27.9)	18 (29.0)	
T3	41 (20.7)	31 (22.8)	10 (16.1)	
T4	6 (3.0)	3 (2.2)	3 (4.8)	
Clark level (I–V)				0.107†
I	11 (5.7)	4 (3.0)	7 (11.7)	
II	4 (2.1)	3 (2.3)	1 (1.1)	
III	18 (9.4)	15 (11.4)	3 (5.0)	
IV	131 (68.2)	92 (69.7)	39 (65.0)	
V	28 (14.6)	18 (13.6)	10 (16.7)	
Positive SLN	35 (16.9)	27 (18.9)	8 (12.5)	0.258†
Ulceration	49 (23.9)	40 (28.4)	9 (14.1)	0.026†
Unplanned reexcision	39 (18.8)	23 (16.1)	16 (25.0)	0.129†

*Student's *t* test.
†χ^2 Test.
BMI, Body Mass Index; N/A, Not Applicable; SLN, Sentinel Lymph Node.

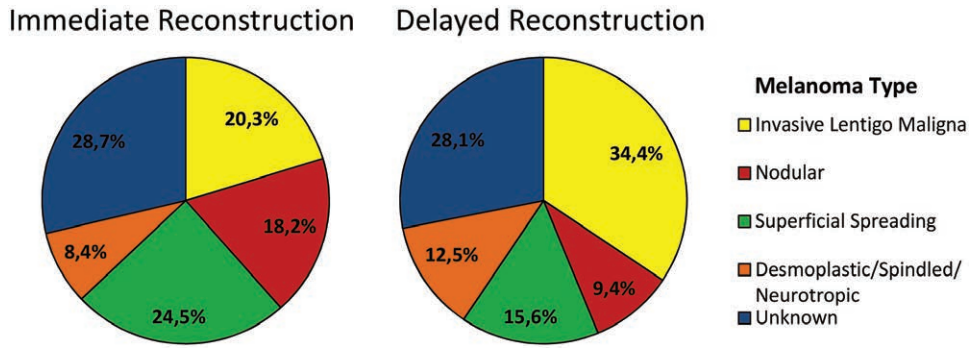

Fig. 1. Melanoma type.

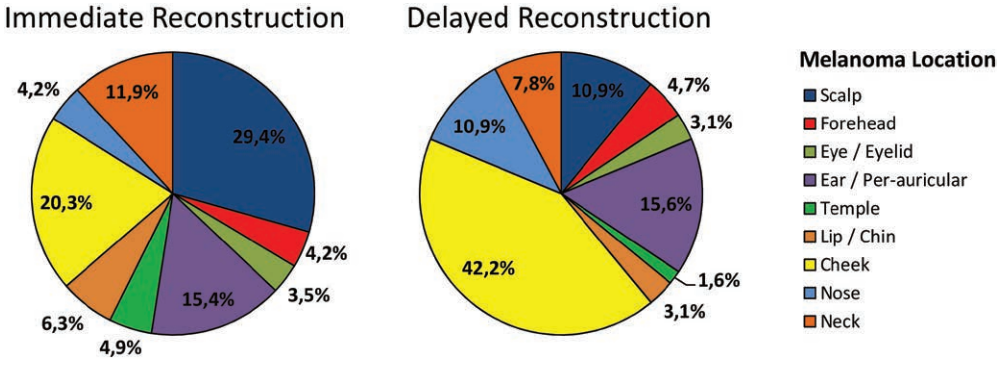

Fig. 2. Melanoma location.

melanoma was performed in all cases of positive tumor margins. Within the delayed reconstruction group, the interval for reconstruction was 8.9 days on average.

Overall, there was no significant association between reconstruction type and recurrence ($P = 0.456$). In this series, skin grafting (41.3%) was the most common form

of immediate reconstruction, whereas local skin flap advancement (59.4%) was the most predominant delayed technique. As presented in Table 2, subset analysis of our recurrence group demonstrated no significant difference in distribution among reconstruction types ($P = 0.103$).

Recurrence and Recurrence-Free Survival

At the end of the follow-up period, 85 patients were observed to have a recurrence after WLE of primary HNCMM. Median time to recurrence was 48.2 months (95% CI, 42.99–53.46), with overall recurrence-free survival rates of 0.834 (95% CI, 0.776–0.878) and 0.549 (95% CI, 0.469–0.622) at 1 and 5 years following reconstruction. Specifically, 70 recurrences were observed in the immediate group, whereas 15 recurrences occurred in the delayed treatment group. Local recurrence was found to be most prevalent (43.5%), followed by distant (20.0%) and nodal recurrence (16.5%). Nevertheless, univariate subgroup analysis did not reveal any significant difference between local ($P = 0.399$), regional ($P = 0.197$), nodal ($P = 0.685$), or distant ($P = 0.477$) recurrences among groups. Details on local, regional, nodal, and distant recurrences are presented in Table 3. Ulceration was found to be significantly more present in patients experiencing recurrence compared with patients who remained recurrence-free (33.7% versus 17.2%; $P < 0.006$). In addition, patients experiencing recurrence were more likely to present with a positive sentinel lymph node (SLN) initially (30.6% versus 7.4%; $P < 0.001$).

Subgroup analysis on patients with local recurrence demonstrated 1-year and 5-year cumulative local recurrence-free survival estimates in the 143 patients undergoing immediate reconstruction to be 0.803 (95% CI, 0.727–0.859) and 0.474 (95% CI, 0.379–0.562), respectively. In comparison, local recurrence survival estimates in the 64 patients receiving delayed reconstruction were 0.905 (95% CI, 0.801–0.956) and 0.734 (95% CI, 0.596–0.832). Local recurrence-free survival was comparable between patients who underwent immediate and delayed reconstruction upon univariate analysis by log-rank test ($P = 0.065$; Fig. 3). After adjusting for melanoma prognostic factors including gender, age, Breslow depth, ulceration, melanoma type, and the presence of a positive SLN during surgery,[16,17] overall multivariate Cox regression analysis also did not demonstrate a significant association between reconstruction timing and recurrence-free survival ($P = 0.167$). Ulceration ($P = 0.040$, hazard ratio, 2.21) and a positive SLN ($P < 0.001$, hazard ratio, 4.30) served as independent risk factors for melanoma recurrence (Fig. 4). Proportional hazard testing confirmed our statistical model met the assumption of proportional hazards (global test, $P = 0.901$).

DISCUSSION

The incidence of malignant melanoma is rapidly increasing more so than any other type of cancer, with men having an increased lifetime risk of developing cutaneous melanoma compared with women.[20] Prognosis is depending greatly on melanoma staging. Stage 1 melanoma has a 5-year survival of 91–95%, stage 2, 45–79%, stage 3, 30–70%, and stage 4 has reported 5-year survival rates of 10–20%.[21]

There is an ongoing debate on the safety of immediate reconstruction following excision of HNCMM, as studies have demonstrated inconsistent results with regard to recurrence. Patients may prefer immediate reconstruction to

Table 2. Reconstruction Type in Patients with Recurrent Melanoma

Characteristics	Total (%)	Immediate (%)	Delayed (%)	*P*
Number of patients	85	70 (49.0)	15 (23.4)	0.167*†
Reconstruction Type				0.103‡
Primary closure	6 (7.1)	6 (8.6)	N/A	
Skin graft	38 (44.4)	35 (50.0)	3 (20.0)	
Skin flap	34 (40.0)	24 (34.3)	10 (66.7)	
Combination	7 (8.2)	5 (7.1)	2 (13.3)	

*χ^2 Test.
†*P* value adjusted for gender, age, Breslow depth, ulceration, melanoma type, and the presence of a positive SLN during surgery.
‡Fisher's exact test.
N/A, Not Applicable.

Table 3. Recurrence Rates

	Total (%)	Immediate (%)	Delayed (%)	P
Total recurrences (n)	85 (41.1)	70 (49.0)	15 (23.4)	0.167*†
Local recurrence	37 (43.5)	29 (41.4)	8 (53.3)	0.399*
Median time to recurrence in months, range		14.5, 0.7–117.8	24.0, 2.5–36.5	
Regional recurrence	10 (11.8)	10 (14.4)	0	0.197‡
Median time to recurrence in months, range		24.2, 5.9–97.5	N/A	
Nodal recurrence	14 (16.5)	11 (15.7)	3 (20.0)	0.685‡
Median time to recurrence in months, range		10.0, 2.0–42.8	6.6, 1.3–7.0	
Distant	17 (20.0)	13 (18.6)	4 (26.7)	0.477‡
Median time to recurrence in months, range		32.6, 8.7–75.0	26.9, 6.9–43.0	
Other (local/regional, local/nodal, nodal/regional)	7 (8.2)	7 (10.0)	0	0.344‡
Median time to recurrence in months, range		21.0, 5.7–97.5	N/A	

*χ^2 Test.
†*P* value adjusted for gender, age, Breslow depth, ulceration, melanoma type, and the presence of a positive SLN during surgery.
‡Fisher's exact test.
N/A, Not Applicable.

avoid a second surgery associated with more anesthetic episodes and extra medical costs. In contrast, plastic surgeons may prefer delayed closure with the purpose of preserving the opportunity for additional excision before final reconstruction of the defect. Concerns related to higher local recurrence rates following immediate reconstruction have prompted surgeons to delay their reconstructions until after review of final pathology and confirmation of negative margins.[2,3] In accordance with Sullivan et al.[4], our study presents comparable rates of positive margins after WLE between immediate and delayed reconstruction. A recent study published by Parrett et al.[22] also demonstrate favorable recurrence rates after WLE of HNCMM followed by immediate reconstruction, with low positive margin rates, supporting the safety of immediate reconstruction. However, although studies have presented valuable data supporting the safety of immediate reconstruction following WLE, thus far sample sizes have generally been modest, with limited consistent long-term follow-up.[3,9,11,22,23]

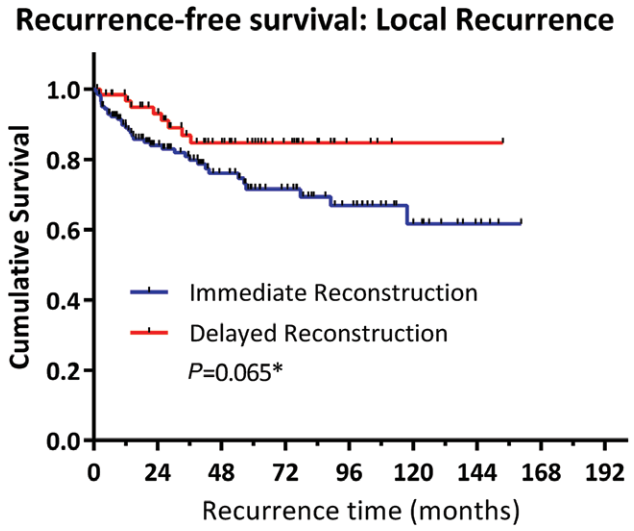

Fig. 3. Recurrence-free survival: local recurrence.

Wide surgical excision followed by a staged reconstruction procedure can result in a desiccated, fibrous, colonized, and/or contracted wound bed. Therefore, this approach may result in a challenge with creating an optimal setting for reconstruction. In this study, we did not find an association between reconstruction timing (immediate versus delayed) after WLE of HNCMM and recurrence-free survival.

There was no significant difference in reconstruction techniques among patients experiencing melanoma recurrence. Regardless, immediate reconstruction is only recommended if it leaves a reasonable option for secondary reconstruction in case of positive margins. The presence of ulceration and a positive sentinel lymph node serve as significant predictors for melanoma recurrence. These findings are consistent with current reports in the literature.[4,23,24] Although the presence of ulceration is a predictive marker for response to adjuvant interferon therapy, it is negatively associated with survival in cutaneous melanoma.[25]

Even though both study cohorts were comparable in demographic and clinical characteristics, this study is subject to the limitations of any retrospective study; lack of follow-up documentation resulted in a fairly high rate

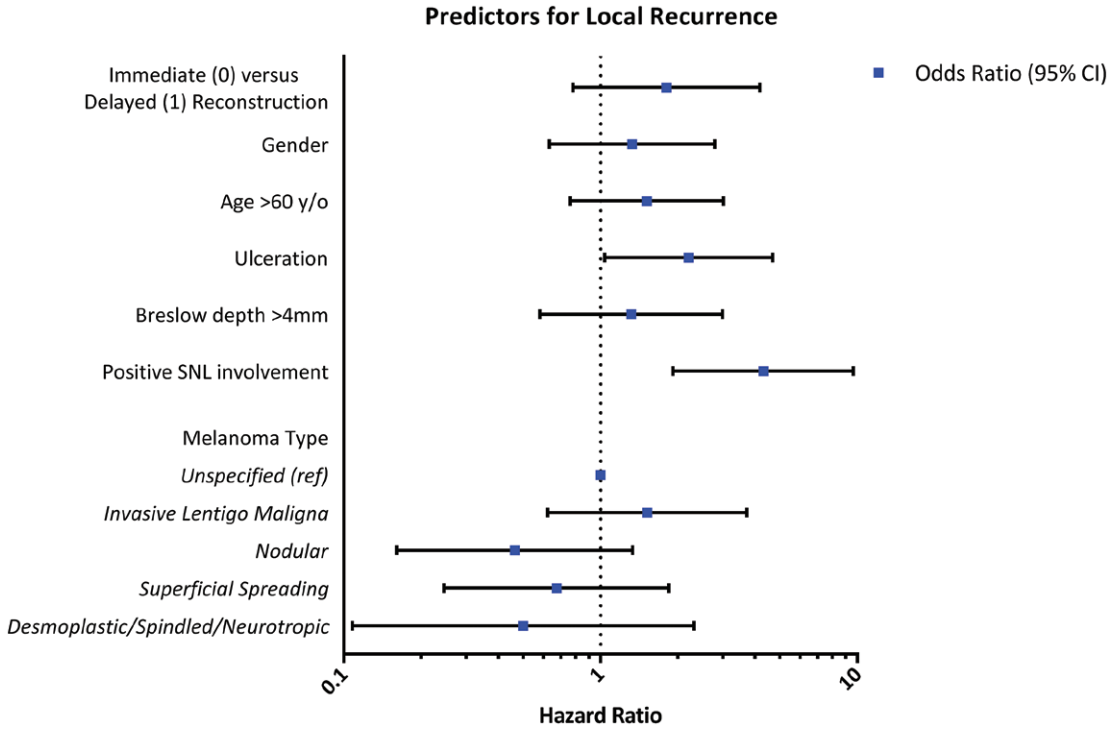

Fig. 4. Forest plot: predictors for local recurrence.

of patient exclusion. Furthermore, due to the retrospective character of the study, we were not able to randomize patients. Initially, we present the reader with unadjusted associations between categorical variables. These tests help to guide the direction of the more rigorous analyses. However, to increase the impact of the data, a multivariable Cox regression analysis is warranted to correct for potential confounders. Lastly, to maintain sufficient power, this study did not allow for subgroup analysis assessing recurrence-free survival rates for different anatomical locations in the head and neck area. To confirm our results and overcome these limitations, a future prospective randomized trial with fair sample size should be performed specifying associations between melanoma location and recurrence rates with regard to reconstruction timing.

CONCLUSIONS

In summary, the rate of positive tumor margins were similar between immediate and delayed reconstruction following WLE. Multivariate regression analysis did not reveal a significant association between reconstruction timing and local recurrence-free survival when acknowledging melanoma prognostic factors, suggesting recurrence-free survival to be independent of reconstruction timing after WLE of primary HNCMM.

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