RESEARCH ARTICLE

Conservative Neck Dissection in Oral Cancer Patients: a 5 Year Retrospective Study in Malaysia

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Abstract

Objective: The impact of ablative oral cancer surgery was studied, with particular reference to recurrence and nodal metastasis, to assess survival probability and prognostic indicators and to elucidate if ethnicity influences the survival of patients. Methods: Patients who underwent major ablative surgery of the head and neck region with neck dissection were identified and clinical records were assessed. Inclusion criteria were stage I-IV oral and oropharyngeal malignancies necessitating resection with or without radiotherapy from 2004 to 2009. All individuals had a pre-operative assessment prior to the surgery. The post operative assessment period ranged from 1 year to 5 years. Survival distributions were analyzed using Kaplan-Meier curves. Results: 87 patients (males:38%; females:62%) were included in this study, with an age range of 21-85 years. Some 78% underwent neck dissections while 63% had surgery and radiotherapy. Nodal recurrence was detected in 5.7% while 20.5% had primary site recurrence within the study period. Kaplan-Meier survival analysis revealed that the median survival time was 57 months. One year overall survival (OS) rate was 72.7% and three year overall survival rate dropped to 61.5%. On OS analysis, the log-rank test showed a significant difference of survival between Malay and Chinese patients (Bonferroni correction p=0.033). Recurrence-free survival (RFS) analysis revealed that 25% of the patients have reached the event of recurrence at 46 months. One year RFS rate was 85.2% and the three year survival rate was 76.1%. In the RFS analysis, the log-rank test showed a significant difference in the event of recurrence and nodal metastasis (p<0.001). Conclusion: Conservative neck is effective, in conjunction with postoperative radiotherapy, for control of neck metastases. Ethnicity appears to influence the survival of the patients, but a prospective trial is required to validate this.

Keywords: Nodal metastasis - oral squamous cell carcinoma - neck dissection - recurrence - Malaysia

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Introduction

The global yearly incidence of head and neck cancer is about 500,000 new cases and increasing numbers of patients are presenting with primary advanced disease not amenable to immediate surgery (Grabenbauera et al., 2003). The treatment of oral cancer is principally directed to the control of locoregional disease because it has been estimated that only 4% of patients with oral cancer die of distant metastases (Cunningham et al., 1986). The incidence of regional lymph node metastasis in oral carcinoma varies from 6% to 85% (Martin et al., 1951; Lindberg, 1972; Shah et al., 1981; Chu and Strawitz, 1987 ; Yirmibesoglu et al., 2012) and its significance as a critical independent prognostic factor in head and neck cancer has long been appreciated.

Although 19th century surgeons attempted to remove involved cervical lymph nodes at the time of resection of the primary cancer, a systematic approach to en bloc removal of cervical lymph node disease, described in detail by Jawdyn´ski in 1888 and popularized and illustrated by Crile (1906) in the early 20th century, provided consistent and more effective treatment, and forms the basis of our current techniques. The greatest impetus to the status of radical neck dissection (RND) came from Martin (1951), whose technique consisted of resection of all lymph nodes from level I-V together with the accessory nerve, internal jugular vein, sternocleidomastoid muscle and various other structures in a single block of resected tissue. This radical surgery has as its aim the "en bloc" dissection of the primary cancerous lesion and the neck lymph nodes to which the tumour has or will metastasize. Martin's technical precepts were followed until the latter part of the 20th century when modifications in technique began to find general acceptance. The first description of an effective technique of modified radical neck dissection (MRND) was published in Spanish by Sua´rez (1963). This technique, which preserves important structures, such as the internal jugular vein, sternocleidomastoid muscle and accessory nerve, was refined and popularized

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by various other authors.

To develop uniformity regarding nomenclature, Robbins et al. (1991) developed standardized neck dissection terminology. Their classification is based on the following concepts: 1) the RND is the fundamental procedure with which all other neck dissections are compared; 2) MRND denotes preservation of 1 or more nonlymphatic structures such as the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. As such, lymph node levels I–V are removed in this neck dissection. Typically, a type I MRND involves preservation of the spinal accessory nerve, a type II MRND involves preservation of the spinal accessory nerve and the internal jugular vein, and a type III MRND involves preservation of the spinal accessory nerve, internal jugular vein, and the sternocleidomastoid muscle.; 3) selective neck dissections (SND) denote preservation of 1 or more group(s) of lymph nodes; and 4) extended RND denotes removal of 1 or more additional lymphatic and/or nonlymphatic structure(s).

Conflicting rationales exist regarding the most appropriate therapeutic management of a clinically negative neck. Results of studies on the nodal pattern of spread of squamous cell carcinoma (SCC) of the oral cavity showed that regional metastases are generally located in levels I–III, while the risk of a levels IV or V lymph node metastasis is extremely low (Mohamed et al., 2008). Therefore, supraomohyoid neck dissection (SOHND), which refers to the removal of lymph nodes contained in levels I–III, has become the standard of care for elective management of clinically N0 necks in patients with SCC of the oral cavity. Kolli et al. (2000) reported that SOHND in patients with pathologically positive nodes in the neck was inadequate for regional control without postoperative radiation therapy. In the absence of factors that violate the fascial compartments of the neck or disrupt lymphatic flow, such as massive adenopathy or gross extracapsular spread, the rationale behind this procedure remains viable. Kerrebijn et al. (1999) found that SOHND is inadequate for clinically positive neck disease due to the higher risk of metastases in level IV; therefore, MRND was recommended for such cases. Medina and Byers (1989) suggested that SOHND is primarily indicated for patients with T2, T3, and T4N0, and selected N1 oral SCC. Spiro et al. (1996) reported that therapeutic SOHND in conjunction with postoperative radiation therapy is highly effective in controlling N1, N2a and N2b.

In terms of prognosis there has been no substantial improvement for these patients; this led to a more critical discussion of turnout surgery with regard to both indications and results. There is a distinct paucity of published literature reporting on oral cancer survival in the South East Asian region, particularly in Malaysia. Historically, patients have been referred to various specialities, non- surgical and surgical, offering a variety of treatment regimes and this wide dispersal of patients and the lack of defined treatment protocols explain the scarcity of reliable data on patient management and survival. Since early 2001, the Department of Oral Surgery at Kuala Lumpur Hospital, Malaysia, has adopted a standard policy for the management of oral cancer. The majority of patients are treated by primary radical surgery including function-preserving neck dissection (MRND) and the resulting defects are reconstructed primarily with or without free tissue transfer.

In this study, we intend to describe the impact of ablative oral cancer surgery with particular reference to recurrence and nodal metastasis. The aim of the present study was to assess the value of these surgical procedures in terms of survival probabilities and prognostic factors and to elucidate if ethnicity influences the survival of the patients.

Materials and Methods

We reviewed our institutional experience with patients who underwent ablative cancer surgery of the head and neck region from 1st January 2005 to 31st December 2009. Notes were retrieved to determine demographic details, site, stage, surgery specifics and follow up outcomes. Records detailing the assessments were accessed and the information collated. Inclusion criteria for enrolment were stage I-IV oral and oropharyngeal malignancy necessitating resections with or without radiotherapy. All individuals had a pre-operative assessment prior to the surgery and presented in a multidisciplinary team conference. TNM status and clinical stages of oral cancer were determined according to the AJCC TNM staging system. The post operative assessment period ranges from 1 year to 5 years. Neck disease-free survival was defined as the interval between the date of the neck dissection and the date of the last consultation or neck recurrence. Only patients who underwent ablative oral cancer surgery were included in this audit. When indicated, neck dissection patients underwent the MRND type I, II or III. All the resection specimens are assessed by a single pathologist using a standard protocol and patients are selected for post-operative radiotherapy on the basis of detailed pathological staging.

The pattern and frequency of recurrence and survival were analysed with respect to the nodal status. Recurrence-free survival (RFS) and overall survival (OS) were the end points in this study. RFS was measured from date of surgery to the first date of documented recurrence and was censored at the date of last follow-up (as of December 2009). OS time was calculated from the date of surgery to the date of death and censored by the last date of follow-up (as of December 2009). The method of Kaplan-Meier was used to evaluate OS and RFS, and the log-rank test was used for comparison analysis. The Cox proportional hazard model was used to estimate the hazard ratios for univariable analysis with the variables included gender, race, T-staging, neck dissection, site, radiotherapy and nodal metastasis. Hazard ratios indicating the effects of prognostic factors on the risk of event (death or recurrence) were calculated and presented with 95% confidence intervals (CI). The Cox model was then carried out for multivariable analysis including all variables with a p-value lowers than or equal to 0.25 in univariable analysis. The reported p-values were based on two-sided tests, and p-values less than 0.05 were considered statistically significant. All statistical analyses

used PASW Statistics version 18 (SPSS Inc, Chicago, IL, USA).

Results

Review of cohort surgical database identified 87 patients diagnosed with oral squamous cell carcinoma, salivary gland malignancies or sarcoma. All surgical procedures were performed by the senior author (WMWM). These patients were in the age range of 21-85 years. Males constituted 33 patients (38%) while females 54 patients (62%). 78% patients underwent neck dissections while 63% patients had surgery and radiotherapy. Nodal recurrence was detected in 5.7% of the patients. 20.5% of the patients had primary site recurrence within the study period. The overall median survival was at 57 months.

In the analysis of OS and RFS, 1 case was excluded as the date of surgery could not be ascertained. The overall survival analysis was based on 28 deaths among the 86 patients (32.6%). The Kaplan-Meier survival analysis revealed that the median survival time was 57 months. One year OS rate was 72.7% and three year OS rate dropped to 61.5% (Figure 1).

The analysis of RFS was based on 18 events among 86 patients (20.9%). The Kaplan-Meier RFS analysis

Table 1. Regression Analysis on RFS and OS

Variable		No. of event (%)	Crude HR	(95% CI HR)	X^2 stat. (df)[a]	P-value[a]	Adjusted HR*	(95% CI HR)	X^2 stat. (df)[a]	P-value[a]
Regression analysis on RFS;										
Age (year)			0.99	(0.96, 1.02)	0.42 (1)	0.515				
Gender:	Female	10/53 (18.9)	1	-	-	-				
	Male	8/33 (24.2)	1.6	(0.63, 4.05)	0.97 (1)	0.326				
Race:					1.37 (2)	0.502			2.55 (2)	0.28
	Malay	7/29 (24.1)	1	-	-	-	1.00	-	-	-
	Chinese	3/22 (13.6)	0.45	(0.12, 1.73)	1.36 (1)	0.243	0.34	(0.08, 1.47)	2.09 (1)	0.148
	Indian	8/34 (23.5)	0.83	(0.30, 2.28)	0.14 (1)	0.71	1.21	(0.37, 3.99)	0.10 (1)	0.757
T-staging:					3.45 (3)	0.327			2.68 (3)	0.444
	T1	1/11 (9.1)	1	-	-	-	1.00	-	-	-
	T2	7/24 (29.2)	3.93	(0.48, 32.08)	1.63 (1)	0.201	2.22	(0.26, 18.80)	0.54 (1)	0.464
	T3	3/ 8 (37.5)	4.3	(0.45, 41.48)	1.59 (1)	0.207	2.31	(0.22, 24.47)	0.48 (1)	0.487
	T4	7/43 (16.3)	1.89	(0.23, 15.39)	0.36 (1)	0.551	1.02	(0.12, 8.67)	0.00 (1)	0.988
Neck dissection:	None	3/19 (15.8)	1	-	-	-				
	Yes	15/67 (22.4)	1.71	(0.49, 5.93)	0.72 (1)	0.397				
Site:					0.06 (2)	0.971				
	Tongue	7/36 (19.4)	1	-	-	-				
	Cheek	6/26 (23.1)	0.96	(0.32, 2.85)	0.01 (1)	0.934				
	Alveolus	3/19 (15.8)	0.85	(0.22, 3.28)	0.06 (1)	0.809				
Radiotherapy:	None	4/32 (12.5)	1	-	-	-	1.00	-	-	-
	Yes	14/54 (25.9)	1.94	(0.64, 5.92)	1.37 (1)	0.242	1.07	(0.30, 3.88)	0.01 (1)	0.914
Nodal metastasis:	None	14/82 (17.1)	1	-	-	-	1.00	-	-	-
	Yes	4/ 4 (100.0)	20.87	(5.94, 73.37)	22.44 (1)	<0.001	28.39	(5.64,142.93)	16.46 (1)	<0.001
Regression analysis on OS;										
Age (year)			1	(0.98, 1.03)	0.05 (1)	0.815				
Gender:	Female	16/53 (30.2)	1	-	-	-				
	Male	12/33 (36.4)	1.46	(0.69, 3.10)	0.99 (1)	0.32				
Race:					6.28 (2)	0.043			4.01 (2)	0.135
	Malay	12/29 (41.4)	1	-	-	-	1.00	-	-	-
	Chinese	3/22 (13.6)	0.2	(0.06, 0.70)	6.28 (1)	0.012	0.28	(0.01, 1.06)	3.51 (1)	0.061
	Indian	13/34 (38.2)	0.73	(0.33, 1.60)	0.63 (1)	0.427	0.99	(0.34, 2.76)	0.00 (1)	0.992
T-staging:					2.41 (3)	0.493			0.52 (3)	0.915
	T1	2/11 (18.2)	1	-	-	-	1.00	-	-	-
	T2	8/24 (33.3)	2.19	(0.46, 10.37)	0.98 (1)	0.321	1.52	(0.28, 8.16)	0.24 (1)	0.624
	T3	4/ 8 (50.0)	3.8	(0.69, 20.90)	2.36 (1)	0.124	1.76	(0.28, 10.86)	0.37 (1)	0.545
	T4	14/43 (32.6)	2.37	(0.54, 10.44)	1.29 (1)	0.256	1.74	(0.37, 8.18)	0.49 (1)	0.486
Neck dissection:	None	6/19 (31.6)	1	-	-	-				
	Yes	22/67 (32.8)	1.15	(0.47, 2.84)	0.09 (1)	0.758				
Site:					2.26 (2)	0.323			4.75 (2)	0.093
	Tongue	13/36 (36.1)	1	-	-	-	1.00	-	-	-
	Cheek	11/26 (42.3)	0.96	(0.42, 2.17)	0.01 (1)	0.917	0.45	(0.16, 1.25)	2.34 (1)	0.126
	Alveolus	3/19 (15.8)	0.39	(0.11, 1.38)	2.13 (1)	0.144	0.26	(0.07, 1.02)	3.76 (1)	0.053
Radiotherapy:	None	6/32 (18.8)	1	-	-	-	1.00	-	-	-
	Yes	22/54 (40.7)	2.16	(0.88, 5.34)	2.80 (1)	0.094	2.19	(0.77, 6.21)	2.16 (1)	0.142
Nodal metastasis:	None	25/82 (30.5)	1	-	-	-	1.00	-	-	-
	Yes	3/ 4 (75.0)	3.04	(0.88, 10.50)	3.10 (1)	0.078	5.19	(1.07, 25.31)	4.15 (1)	0.042

*The multivariable analysis was carried out with the selected factors of which p-value<0.25 from the univariable analysis, HR=Hazard Ratio, [a]Wald test of Cox Regression with Enter method

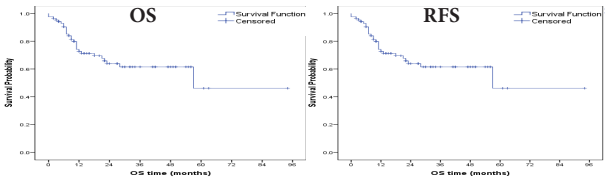

Figure 1. OS and RFS Kaplan-Meier Analysis.

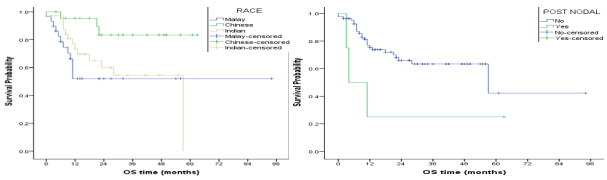

Figure 2. Overall Survival Curve by Race and Nodal Metastasis.

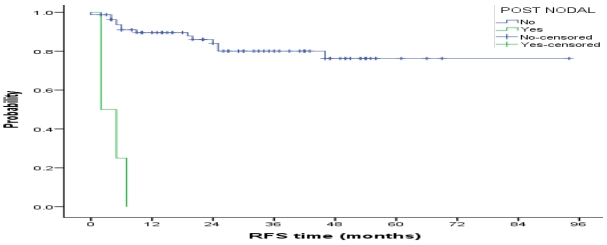

Figure 3. Recurrence-Free Survival Curve by Nodal Metastasis.

revealed that 25% of the patients have reached the event of recurrence at 46 months (median not reached). One year RFS rate was 85.2% and three year survival rate was 76.1% (Figure 1).

In OS analysis (Figure 2), the log-rank test shows a significant difference of survival between Malay and Chinese race groups (Bonferroni correction p=0.033). Among patients with a history of a conservative neck dissection surgery, there were 12 deaths in the 29 Malay patients, and 3 deaths in the 22 Chinese patients. There was no statistically significant association identified in survival experience between gender (log-rank p=0.313), T-staging (log-rank p=0.456), neck dissection (log-rank p=0.756), site (log-rank p=0.293), radiotherapy (log-rank p=0.084), and nodal metastasis (log-rank p=0.064).

In RFS analysis (Figure 3), the log-rank test shows a significant difference in the event of recurrence and nodal metastasis. In this subgroup, all 4 patients with nodal metastasis experienced the event of recurrence, as compared with 14 of the 82 patients without nodal metastasis (p<0.001 by the log-rank test). There is no significant difference in recurrence experience between gender (log-rank p=0.318), race (log-rank p=0.484). T-staging (log-rank p=0.285), neck dissection (log-rank p=0.389), site (log-rank p=0.971), and radiotherapy (log-rank p=0.231).

Regression on RFS (Table 1) showed that among the prognostic factors, patients with nodal metastasis have significantly higher risk of experiencing the event of recurrence as compared to those without nodal metastasis (p<0.001). The risk of having recurrence of those patients with nodal metastasis at the time of surgery is 28.4 times of that of those without nodal metastasis (95% CI: 5.6, 142.9).

Regression on OS (Table 1) showed that among the prognostic factors, patients with nodal metastasis have significantly higher risk of dying as compared to those without nodal metastasis (p=0.042). The risk of dying of those patients with nodal metastasis at the time of surgery is 5.2 times of that of those without nodal metastasis (95% CI: 1.1, 25.3).

In general, the presence of nodal metastasis is a significant prognostic factor in oral cancer patients for both death outcome and the event of recurrence outcome (p=0.042 and p<0.001, respectively).

Discussion

There are general principles in cancer surgery: the performance of a maximum operation for minimal disease, and cure is more likely to occur if microscopic loci of the lesion are removed before gross extensive involvement takes place. The performance of a node clearing procedure, even when the neck is clinically negative, has radically altered the incidence of neck failure from recurrent disease (5.7% in this series). Our incidence of relapse in the negative operated neck is low compared to other studies, (Spiro et al., 1988; Francheschi et al., 1993; Hughes et al., 1993) but our findings emphasise the importance of including Level IV in neck dissections for all tumours involving oral cavity even when the neck is clinically negative.

While dissection of level IV may expose the patient to some risk of chyle fistula, or even phrenic nerve injury, for patients with oral tongue cancer, inclusion of level IV in the dissection appears justified in view of known lymphatic drainage of the tongue and the higher incidence of "skip" metastases (Byers et al. 1997; De Cicco et al., 2006; De Zinis et al., 2006). Byers et al. (1997) reported a high incidence (15.8%) of either level III or IV metastasis as the only manifestation of disease in the neck, without disease in levels I and II, among 277 patients with oral tongue carcinoma. Crean et al. (2003) found an extra 10% of occult metastasis to level IV that would have been missed had they preformed a traditional SOHND in the clinically N0 necks of the 49 cases of oral cancer that they reviewed (Crean et al., 2003).

Although many authors are advocating the use of SND for management of the clinically N0 necks, further evaluation of the technique needs to be done so as not to jeopardize any oncologic benefit. Clayman and Frank (1998) found that, despite clear guidelines, the anatomical boundaries in a SND are not as well defined as in a MRND, leading to increased rate of out-of-field recurrences. This outcome can also be affected by the operator's experience and judgement. Of 4.5% neck recurrences after selective neck dissection, Carvalho et al. (2000) found 57.1% of them to be inside the limits of dissection. Similarly, Anderson et al. (2002) and Chepeha et al. (2002) reported two-thirds of recurrences following SOHND to be in the field of dissection.

Whitehurst and Droulias (1977) reported that 85% of the locoregional recurrences after surgical excision of tongue carcinoma occurred within 1 year, 95% within 2 years and 100% in 3 years. Similarly, for tumours of the floor of the mouth, Fu and colleagues (1976) reported that

90% of the local and regional neck recurrences occurred within the first 2 years. The lower rate of locoregional relapse in our series could be attributed to detection of tumour at an earlier stage, possibly less aggressive variants of oral malignancy and post operative radiotherapy. In the present study, locoregional relapse (20.5%) included a true recurrence developing from residual microscopic foci of tumour cells left in the operative site and a new primary (metachronous) SCC developing from the oral mucosa adjacent to the reconstruction site. All these reports support the importance of close and vigilant follow-up in the early postoperative period, particularly in the first 2 years.

This study shows that the presence of nodal metastasis is a significant prognostic factor in oral cancer patients for both death outcome and the event of recurrence outcome ($p=0.042$ and $p<0.001$, respectively). In terms of prognostic indicators, the finding of this study is consistent with the well established fact that nodal metastasis is a reliable prognosis marker for recurrence and survival.

This study also reveals a significant difference of overall survival between Malay and Chinese race groups (Bonferroni correction $p=0.033$). While the published evidence pertaining to inter- ethnicity survival in scarce, the authors cannot exclude the possibility of earlier presentation among Chinese patients as a contributing factor. A better oral health care awareness and accessibility may have also contributed to this finding. We would recommend a prospective study on a larger sample of multi ethnic patients to further validate this finding.

Other factors such as tumor thickness may be better predictors of occult metastases than size of lesion. In different studies, tumor thickness of 3 mm to 5 mm in oral tongue carcinoma,1.5 mm to 3 mm in floor-of-mouth carcinoma, and above 6 mm in buccal mucosa carcinoma were associated with significantly higher rates of occult metastases (Mohit-Tabatabai et al., 1986, Spiro et al., 1986, Fukano et al., 1997, Urist et al., 1987). Clark et al. (2006) reported 10% and 46% incidence of regional disease in thin (<5 mm) and thick (>5 mm) tumors, respectively.

The authors cannot exclude the possibility of some unknown anatomical structure that predispose the tumour to be more aggressive in this region. An unusually aggressive course and frequent extracapsular spread of metastases has been described in regional lymph nodes. Other clinicopathologic factors significantly associated in multivariate studies with the development of cervical lymph node metastasis have been the presence of perineural invasion, an infiltrating-type invasion front, and poorly differentiated tumors. Occult metastasis is another factor that should not be overlooked. Rates of occult metastatic nodes have been reported in 18% to 53% of T1 to T2 oral tongue carcinomas, (Lydiatt et al., 1993; Haddadin et al., 1999) 17% to 37% of T1 to T2 floor-of-mouth carcinomas (Mohit-Tabatabai et al., 1986, McGuirt et al., 1995, Nason et al., 1990) and 26% of T2 or greater buccal mucosa carcinomas (Diaz et al., 2003).

When new and highly sensitive investigations that may detect subpathological as well as subclinical disease are employed, the incidence of metastases detected has been found to be higher than previously indicated. These newer technologies which include immunohistochemistry (Michikawa et al., 2012), molecular analysis and ultrasound-guided fine needle aspiration (Sureshkannan et al., 2011) would be instrumental in better staging and monitoring of potential recurrence.

In conclusion, the philosophy of optimal neck dissection continues to evolve as surgeons realize that more extensive surgery does not necessarily equate to a better oncologic outcome. Multi-institutional prospective studies of clinical outcomes are necessary to definitively determine the therapeutic efficacy of SND compared to MRND in the treatment of patients with clinically positive lymph nodes. Our ability to perform studies of this type has been complicated by the need for a fully executed informed consent, which often persuades patients to choose a more conventional approach. It is imperative to foresee that neck recurrence might be beyond salvage, thus it is better to control the neck disease in the first place. This concept further stands for aggressive postoperative radiation therapy. It is also our belief that the surgeon should make every effort to eradicate all disease whenever possible rather than leave a small residual disease and hope for adjuvant treatment to control the disease.

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