HHS Public Access

Author manuscript

Head Neck. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Head Neck. 2019 June ; 41(6): 1935–1942. doi:10.1002/hed.25633.

Depth of Invasion Alone as an Indication for Post-operative Radiotherapy in Small Oral Squamous Cell Carcinomas: An International Collaborative Study

Ardalan Ebrahimi, MBBS, MPH[1,2,3,4], **Ziv Gil, MD, PHD**[5,6], **Moran Amit, MD**[5,6], **Tzu-Chen Yen, MD**[7], **Chun-ta Liao, MD, PHD**[7], **Pankaj Chaturvedi, MD**[8], **Jai Prakash Agarwal, MD**[8], **Luiz P Kowalski, MD, PHD**[9], **Hugo F Köhler, MD**[9], **Matthias Kreppel, MD, PHD**[10], **Claudio R Cernea, MD, PHD**[11], **Jason Brandao, MD**[11], **Gideon Bachar, MD**[12], **Andrea Bolzoni Villaret, MD**[13], **Dan M Fliss, MD**[14], **Eran Fridman, MD**[14], **K Thomas Robbins, MD**[15], **Jatin P Shah, MD**[16], **Snehal G Patel, MD**[16], **Jonathan R Clark, MBBS, MD**[1,4,17], and **The International Consortium for Outcome Research (ICOR) in Head and Neck Cancer**

[1]Sydney Head and Neck Cancer Institute, Royal Prince Alfred Hospital, Sydney, NSW, Australia

[2]Department of Head and Neck Surgery, The Canberra Hospital, Canberra, ACT, Australia

[3]Australian School of Advanced Medicine, Macquarie University, Sydney, NSW, Australia

[4]University of New South Wales, Sydney, NSW, Australia

[5]The Laboratory for Applied Cancer Research

[6]Department of Otolaryngology Rambam Medical Center, Rappaport School of Medicine, the Technion, Israel institute of technology, Haifa, Israel

[7]Chang Gung Memorial Hospital, Taoyuan, Taiwan

[8]Tata Memorial Hospital, India

[9]Hospital A.C. Camargo, São Paulo, Brazil

[10]Department of Oral and Cranio-Maxillo and Facial Plastic Surgery University of Cologne, Germany

[11]Department of Head and Neck Surgery, University of São Paulo Medical School, São Paulo, Brazil

[12]Department of Otolaryngology Head and Neck Surgery, Rabin Medical Center, Petach Tikva, Israel

[13]Department of ENT, University of Brescia, Italy

[14]Department of Otolaryngology Head and Neck Surgery, Tel Aviv Medical Center, Tel Aviv, Israel

Correspondence: Ardalan Ebrahimi MBBS, FRACS, MPH. Department of Head & Neck Surgery, The Canberra Hospital, Canberra, Australia., ardalan@specialistheadandneck.com.

Presentation: this study was presented at the Annual Meeting of the Australian and New Zealand Head & Neck Cancer Society in 2014, Darwin, Australia.

Disclaimers: nil

[15]Southern Illinois University School of Medicine, Illinois, USA

[16]Head and Neck Surgery Service, Memorial Sloan-Kettering Cancer Center, NY, USA

[17]Sydney University, Sydney, NSW, Australia.

Abstract

Background—We aimed to investigate whether depth of invasion (DOI) should be an independent indication for post-operative radiotherapy (PORT) in small oral squamous cell carcinomas (SCC).

Methods—Retrospective analysis of DOI (<5mm, 5-<10mm, ≥10mm) and disease-specific survival (DSS) in a multi-institutional international cohort of 1,409 patients with oral SCC ≤4cm in size treated between 1990–2011.

Results—In patients without other adverse factors (nodal metastases; close [<5mm] or involved margins), there was no association between DOI and DSS, with an excellent prognosis irrespective of depth. In the absence of PORT, the 5-year disease-specific mortality was 10% with DOI ≥10mm, 8% with DOI 5–10mm, and 6% with DOI <5mm (p=.169), yielding an absolute risk difference of only 4%.

Conclusion—The deterioration in prognosis with increasing DOI largely reflects an association with other adverse features. In the absence of these, depth alone should not be an indication for PORT outside a clinical trial.

Keywords

depth of invasion; tumor thickness; oral squamous cell carcinoma; head and neck cancer; radiotherapy; survival; locoregional control

INTRODUCTION

In most institutions, resectable oral squamous cell carcinoma (SCC) is treated with primary surgery with the addition of PORT ± chemotherapy in the presence of adverse pathological features. While there is institutional variation in practice, the generally accepted indications for PORT include compromised surgical margins, locally advanced disease (>4cm in size), the presence of perineural or lymphovascular invasion, poorly differentiated tumors, and N2–3 nodal disease with or without extracapsular spread.[1–3] Although PORT reduces recurrence risk, the extent of benefit needs to be weighed in each patient against healthcare costs, side effects of treatment, and potential for long-term sequelae such as xerostomia, dental caries, dysgeusia, osteoradionecrosis, trismus, lymphoedema, fibrosis and dysphagia.[4]

Depth of invasion (DOI) of the primary tumor is well established as an independent predictor of recurrence and survival in oral SCC[5–18] resulting in its recent inclusion in the 8th edition American Joint Committee on Cancer Staging Manual.[19] This has led a number of authors to suggest that DOI might represent an independent indication for post-operative radiotherapy (PORT) in patients with small (≤4cm) oral SCCs,[6, 20, 21] and indeed a number of institutions have formally adopted this practice.[22, 23]

Depth of invasion is strongly correlated with other adverse pathological features such as perineural invasion,[24, 25] involved or close surgical margins, T classification, N classification, and extracapsular nodal spread (ECS).[18] We hypothesized that the deterioration in prognosis with increasing DOI may largely reflect the association with other poor prognostic factors and that, in the absence of these, DOI alone does not warrant introduction or intensification of adjuvant therapy. The primary aim of this study was to determine if increasing DOI results in significant deterioration in prognosis in patients with small oral SCC in the absence of other adverse pathological features. Our secondary aims were to quantify any observed difference in prognosis and to determine if outcomes differed based on the addition of PORT in patients with thick tumors.

MATERIAL AND METHODS

Study Population

We performed an international multicenter study using pooled individual patient data from 11 comprehensive cancer centers between 1990 and 2011. Patients with histologically confirmed oral SCC ≤4 cm in size undergoing surgical resection of the primary tumor and neck dissection with curative intent were candidates for inclusion. Elective neck dissection was performed in 1002 (71.1%) cases according to institutional protocols. We excluded cases if they had received neoadjuvant therapy, were aged <20 years, experienced peri-operative mortality, or had inadequate information to determine primary depth of invasion, pathological T (pT) category, or pathological N (pN) category. The final study population consisted of 1409 patients. Ethics approval was obtained from local institutional review board committees of participating centers.

Histopathological Analysis

Histopathological assessments were performed by pathologists experienced in the examination of head and neck tumors in each center. Procedures at participating centers were in accordance with guidelines for the histopathological assessment of head and neck carcinoma.

Although many authors use the terms depth of invasion and thickness synonymously, they are not the same and a distinction should be made.[26, 27] Depth of invasion is considered to be the extent of invasion below the epithelial basement membrane.[27] In contrast, tumor thickness is probably best defined according to the definition proposed by Moore *et al*, which extends from the level of adjacent normal mucosa to the deepest point of tumor invasion.[26]

Statistical Analysis

Statistical analysis was performed using Stata version 12.0 SE (StataCorp LP, College Station, TX). All statistics were 2-sided and a value of $p<.05$ was considered statistically significant. Disease-specific survival (DSS) was calculated from the time of primary surgical treatment to death resulting from oral SCC. Patients not experiencing this end point were censored at last follow-up and patients who died from causes other than oral SCC were

censored at the time of death. Locoregional control (LRC) was defined as pathologically proven tumor relapse in the primary site or neck.

Depth of invasion was analysed as a categorical variable with *a priori* classification into three groups (<5 mm, 5 to <10 mm, ≥10 mm) based on approximate tertiles. In addition, depth of invasion was analysed as a continuous variable after logarithmic transformation since the distribution was right skewed. Differences in DSS and LRC based on depth of invasion were determined using univariable Cox regression stratified by study center, and cumulative failure curves generated using the Kaplan-Meier method when appropriate. Planned subgroup analyses were performed based on the presence or absence of any other adverse pathological features (pathologically proven nodal metastases, and/or close [<5 mm] or involved surgical margins) and PORT. Three-way interaction terms between PORT, DOI and presence or absence of adverse features were also used to assess whether the prognostic impact of DOI differed based on whether PORT was administered in those with thick tumors without other adverse features. Multivariate analyses were performed using Cox proportional hazard models, stratified by study center, and adjusted for age, primary tumor size (≤2 cm versus >2–4 cm), pN category (N0, N1, N2, N3), surgical margin status (clear, close [<5 mm], involved), ECS, time period of primary treatment (1990–1999, 2000–2011) and PORT.

RESULTS

Patient Demographics

The study population consisted of 1409 patients with oral SCC, treated at 11 participating tertiary cancer centers from eight countries. There were 1065 men and 344 women, with a median age of 55 years (range: 22–90 years) and median follow-up of 59 months. Relevant demographic and clinicopathological details are summarized in Table 1.

Primary Depth of Invasion

The mean and median DOI were 8.6mm and 7.8mm, respectively. As shown in Table 2, there was a statistically significant association between increasing DOI and other adverse prognostic factors, including primary tumor size ($p<.001$), pN category ($p<.001$), ECS ($p<.001$), and close or involved margins ($p<.001$).

Survival and Locoregional Control

The 5-year DSS for the cohort was 84.9%, with 193 deaths due to oral SCC and 277 locoregional recurrences. As demonstrated in Figure 1, increasing DOI was associated with a statistically significant increased risk of disease-specific mortality ($p<.001$) and locoregional failure ($p=.010$) in univariate analyses, particularly in tumors with DOI ≥10 mm (Table 3). The association with DSS ($p<.001$) and LRC ($p<.001$) remained statistically significant when depth was analyzed as a continuous variable (Table 3). In multivariate analyses, depth remained a significant predictor of DSS, particularly in tumors ≥10mm in depth, and a trend was observed for LRC (Table 3). These analyses were performed to demonstrate that DOI is an independent prognostic factor in this patient cohort, consistent the existing literature on oral SCC.

We then performed preplanned subgroup analyses. In the subset of 132 patients with at least one additional adverse factor who did not receive PORT, increasing DOI was associated with reduced DSS (p=.017). As shown in Figure 2A, the 5-year disease-specific mortality rate was 32% in tumors with DOI≥10 mm, 18% in those between 5–10 mm, and 8% in those with DOI <5 mm. The association between DOI and DSS remained statistically significant in the 507 patients with at least one other adverse factor even when PORT was administered (p=.029). In this group, 5-year disease-specific mortality was 32% with DOI ≥10 mm, 22% with DOI 5–10 mm, and 20% with DOI <5 mm (Figure 2B).

In contrast, in patients with no additional adverse factors, there was no association between DOI and DSS irrespective of whether PORT was administered (N=141; p=.280) or not (N=628; p=.169). Importantly, the absolute rates of death due to oral SCC were very low in this last subset of patients despite single modality therapy, with an excellent prognosis seen even in those with thick tumors. In the absence of PORT, the 5-year disease-specific mortality was 10% in tumors with DOI ≥10 mm, 8% with DOI between 5–10mm, and 6% with DOI <5 mm (Figure 2C). A multivariate analysis was performed in this subgroup (N=628) adjusting for age, primary tumor size and time period of primary treatment and confirmed no difference in DSS based on depth (p=.375). In those that received PORT, the 5-year disease-specific mortality was 12% in tumors with DOI ≥10 mm, 6% with DOI between 5–10mm, and 0% with DOI <5 mm (Figure 2D). Analysis with interaction terms led to similar results, with no difference in DSS based on whether PORT was administered in those with DOI ≥10 mm (p=.481) and DOI 5–10mm (p=.560) in the absence of other adverse features.

As shown in Figure 3, a similar pattern was observed for LRC although, in contrast to DSS analyses, differences based on DOI failed to reach statistical significance in the subset of patients with other adverse prognostic factors. Critical to this study, in tumors with no other adverse features that did not receive PORT, there was no association between LRC and DOI (p=.240). The 5-year cumulative locoregional failure rate was 17% in tumors with DOI ≥10 mm, 15% with DOI between 5–10mm, and 14% with DOI <5 mm (Figure 3C). This confirms a minimal 3% difference in absolute risk of locoregional recurrence based on DOI in this subset of patients. Again, analysis with interaction terms led to similar results, with no difference in LRC based on whether PORT was administered in those with DOI ≥10 mm (p=.775) and DOI 5–10mm (p=.580) in the low risk subgroup.

DISCUSSION

Depth of invasion of the primary tumor is well established as an independent predictor of recurrence and survival in oral SCC[5–18]. Although there is some evidence and institutional support in favor of regarding DOI as an independent indication for PORT in small oral SCCs,[6, 17, 20–23] this remains controversial and the practice has not been widely adopted to our knowledge. In the current multicenter study, the deterioration in prognosis with increasing DOI appeared to be primarily due to the association with other poor prognostic factors. In the absence of pathological nodal metastases or close/involved margins, we found no association between DOI and locoregional failure or disease-specific

mortality with minimal absolute differences in risk based on DOI, irrespective of whether PORT was administered.

In our study cohort, DOI was strongly correlated with other adverse pathological features including involved or close (<5mm) surgical margins, primary tumor size, pN classification, and ECS, which is consistent with previous studies.[18, 24, 25] We confirmed that DOI is a significant predictor of LRC and DSS on both univariate and multivariate analyses. However, we were only able to adjust for a limited number of other potential confounders in the multivariate models due to a lack of complete clinical, pathological and treatment related data.

The central aim of this study was to determine if DOI should represent an independent indication for PORT in small oral SCCs. Therefore, we performed *a priori* planned subgroup analyses, with specific interest in the subset of patients with clear margins and no evidence of pathological nodal metastases, since this group did not have other major indications for PORT and management might therefore be changed.

This low risk subset included 769 patients, accounting for 54.6% of our study population. Despite this, 141 (18.3%) of these patients received PORT, which presumably largely reflects the presence of other adverse prognostic factors which were not available for adjustment in this study, including perineural invasion, lymphovascular invasion, pattern of invasion and tumor differentiation. In the 628 patients treated with surgery alone, there was no association between DOI and LRC (p=.240) or DSS (*p*=.169).

Although a trend towards worse outcomes in patients with thick tumors is observed, it is crucial to interpret this in the context of two factors: power and absolute risk. With 628 patients, 98 locoregional recurrences and 48 disease-related deaths in this group, the study is well powered to detect a clinically relevant difference in LRC and DSS according to DOI grouped into 3 categories. Whilst a larger study may show statistically significant differences based on DOI, this would not be of any clinical relevance given the absolute risks observed. For example, the 5-year disease-specific mortality in this subset of patients was 10% in tumors with DOI ≥10 mm, 8% with DOI between 5–10 mm, and 6% with DOI <5 mm. This represents an absolute difference in risk of 4% between the lowest and highest categories, similar to the 3% observed risk difference for locoregional failure. This highlights the importance of considering absolute levels of risk with many studies focusing only on relative measures such as the hazard ratio. In our view, this does not justify the additional morbidity and cost of PORT. Particularly when one also considers that a proportion of patients experiencing locoregional failure will be salvageable after single modality treatment with surgery and conversely radiotherapy may not prevent locoregional failure in all those at risk. Finally, the small differences in risk observed in this study may reflect residual confounding since we could not exclude patients with certain high-risk features that are often indications for PORT, including perineural invasion, lymphovascular invasion and tumor differentiation.

It is likely that depth of invasion reflects not only underlying disease biology, but also delayed patient presentation. Hence, a subset of patients with thicker primary tumors may have relatively biologically indolent disease but present with thick tumors due to delayed

presentation and diagnosis, but this needs to be explored in future studies. It would be of clinical interest to determine if such tumors are associated with pushing rather than discohesive advancing fronts, since the former are known to carry a more favorable prognosis.[28–30]

This study has several strengths including a large sample size and international multicenter design that should strengthen the generalizability of our findings, however, several limitations must be acknowledged. Firstly, it was performed using a combination of prospectively and retrospectively collected data, and treatment was not assigned in a randomized fashion. Secondly, we lacked tumor subsite data and cannot exclude the possibility that the implications of DOI for treatment may differ between subsites, particularly the oral tongue. Thirdly, we lacked data on perineural invasion, lymphovascular invasion, and tumor differentiation, however as discussed we believe the results would be strengthened if this data were available since a more truly low risk subgroup could be defined. Fourthly, there is likely to be variability among institutions over the extended time period of the study in terms of pathology protocols used to assess depth of invasion and inter-observer variability among pathologists. Finally, it may be useful for future studies to look specifically at the end point of local failure rather than the composite of locoregional failure.

In conclusion, our results show that the deterioration in prognosis with increasing depth of invasion reflects an association with other poor prognostic factors. In the absence of these other features, depth alone should not be an indication for PORT outside of a clinical trial setting.

Acknowledgments

Grant support: P30 CA008748

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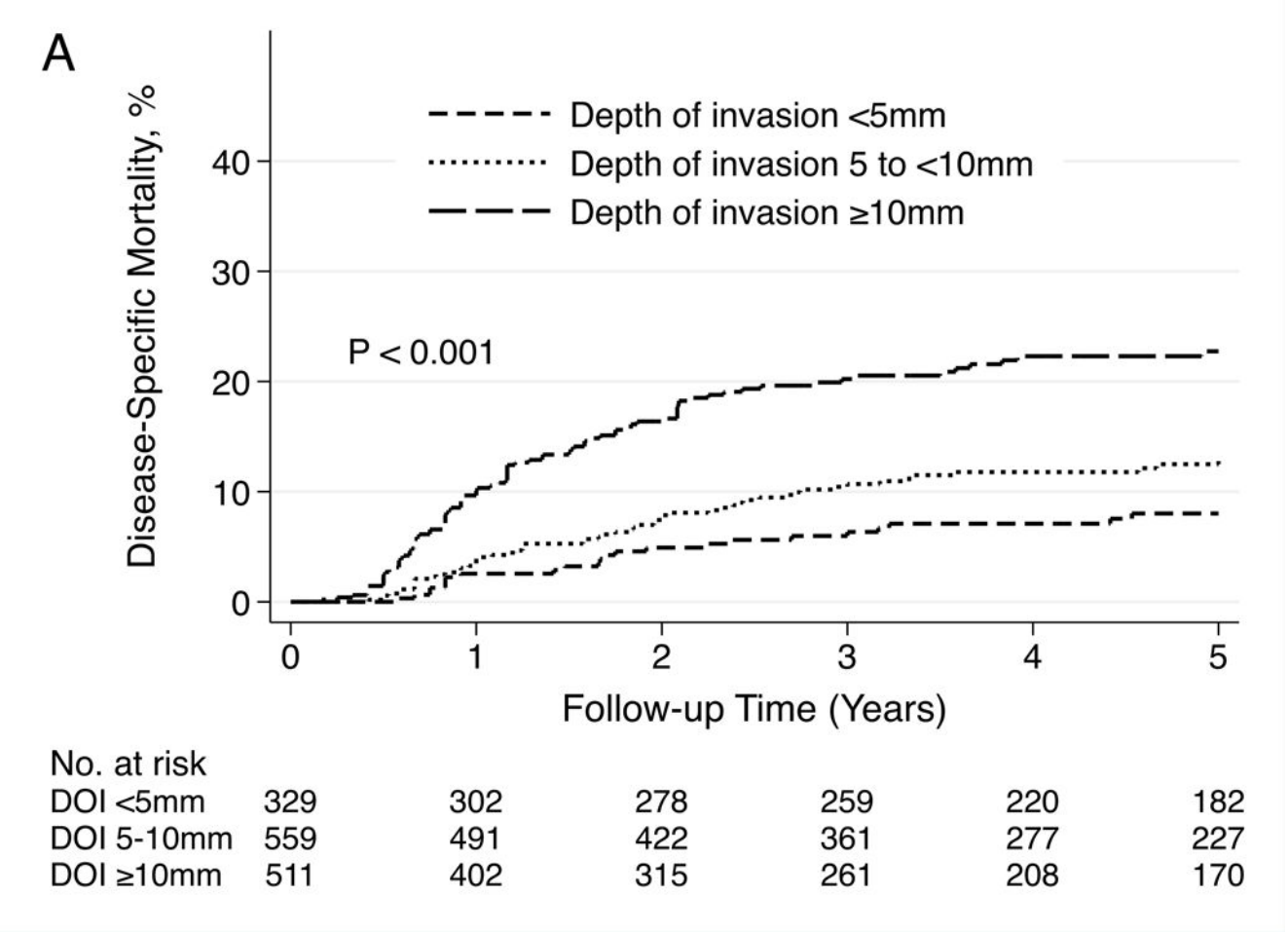


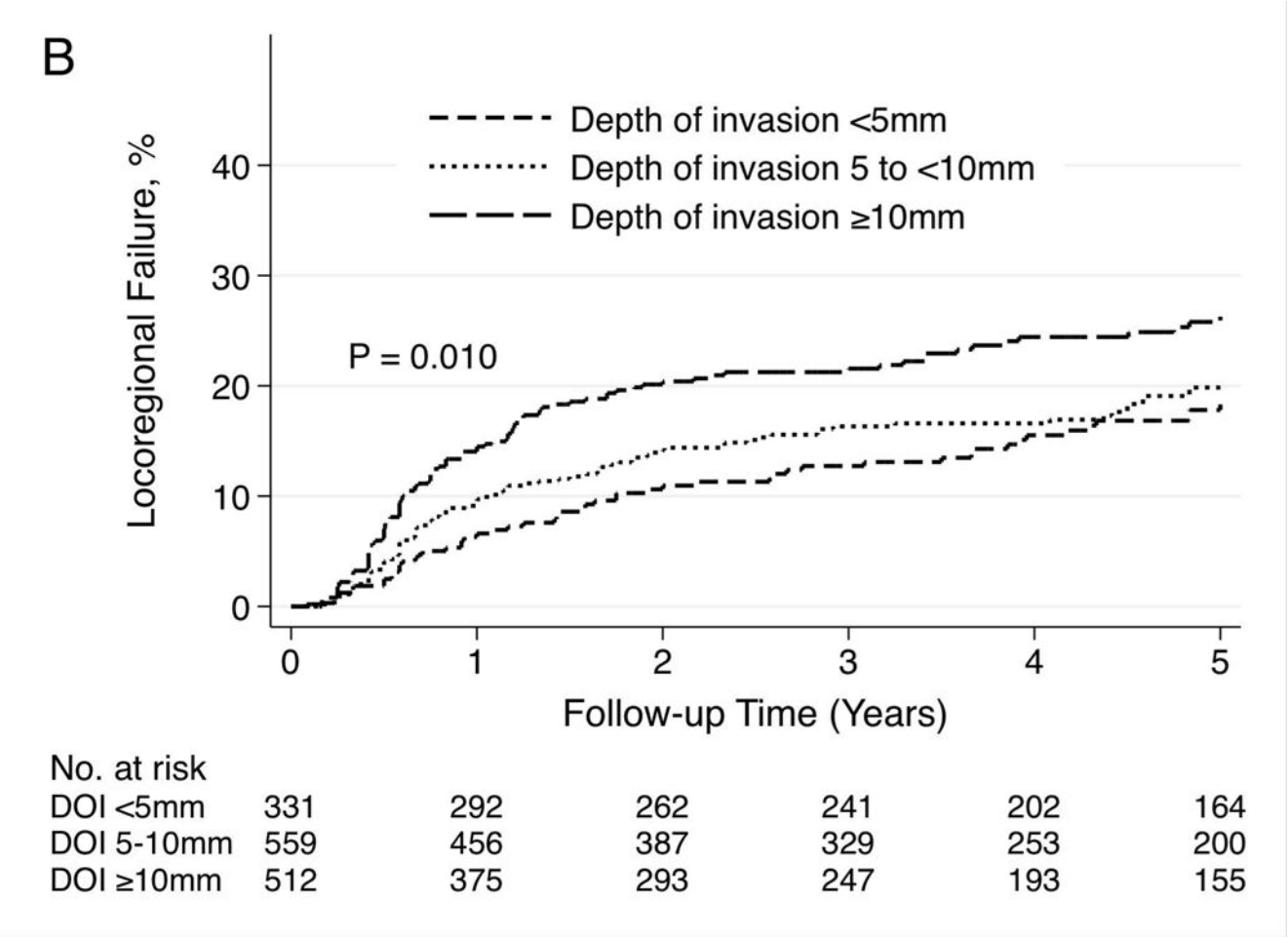
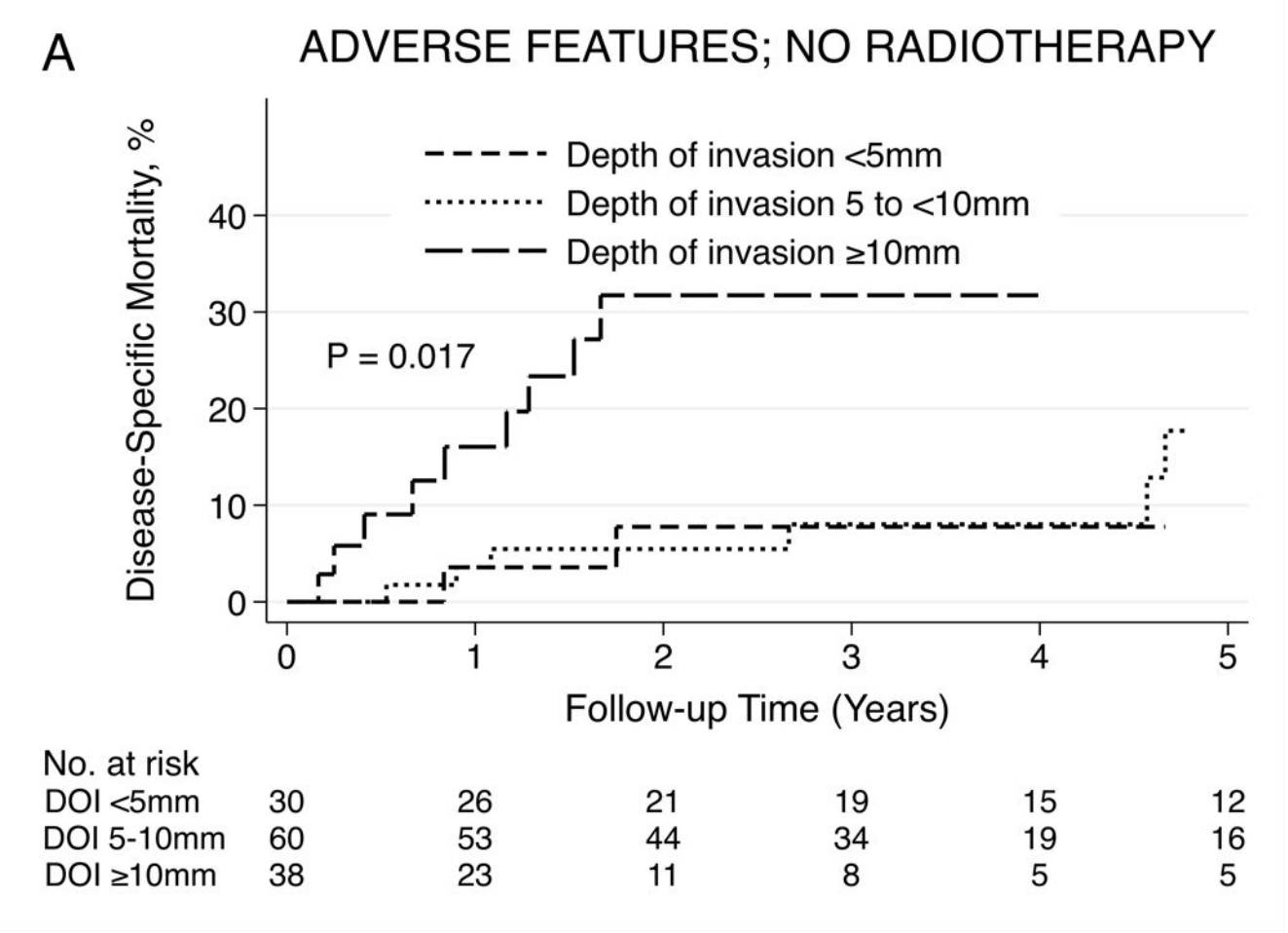
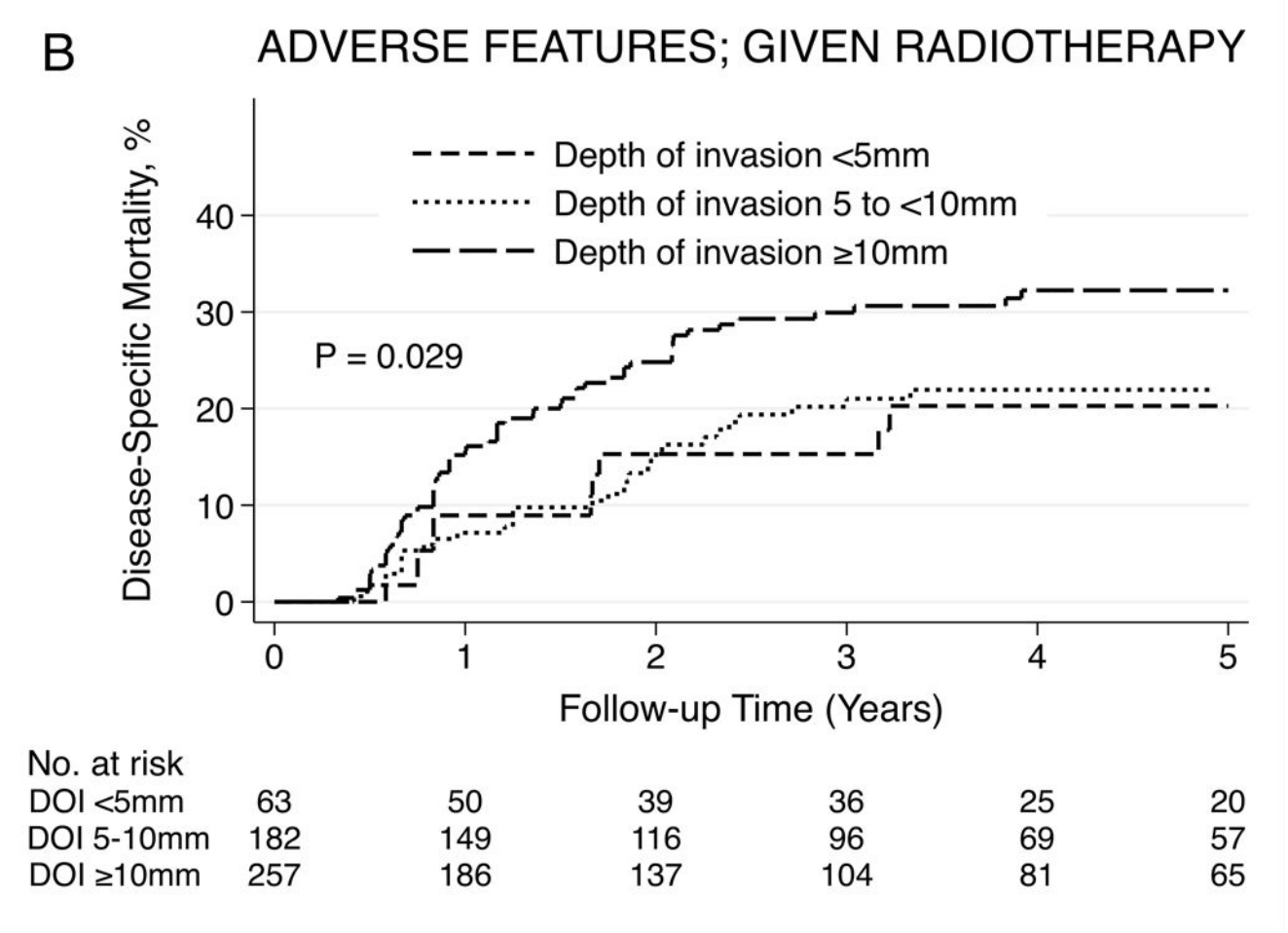
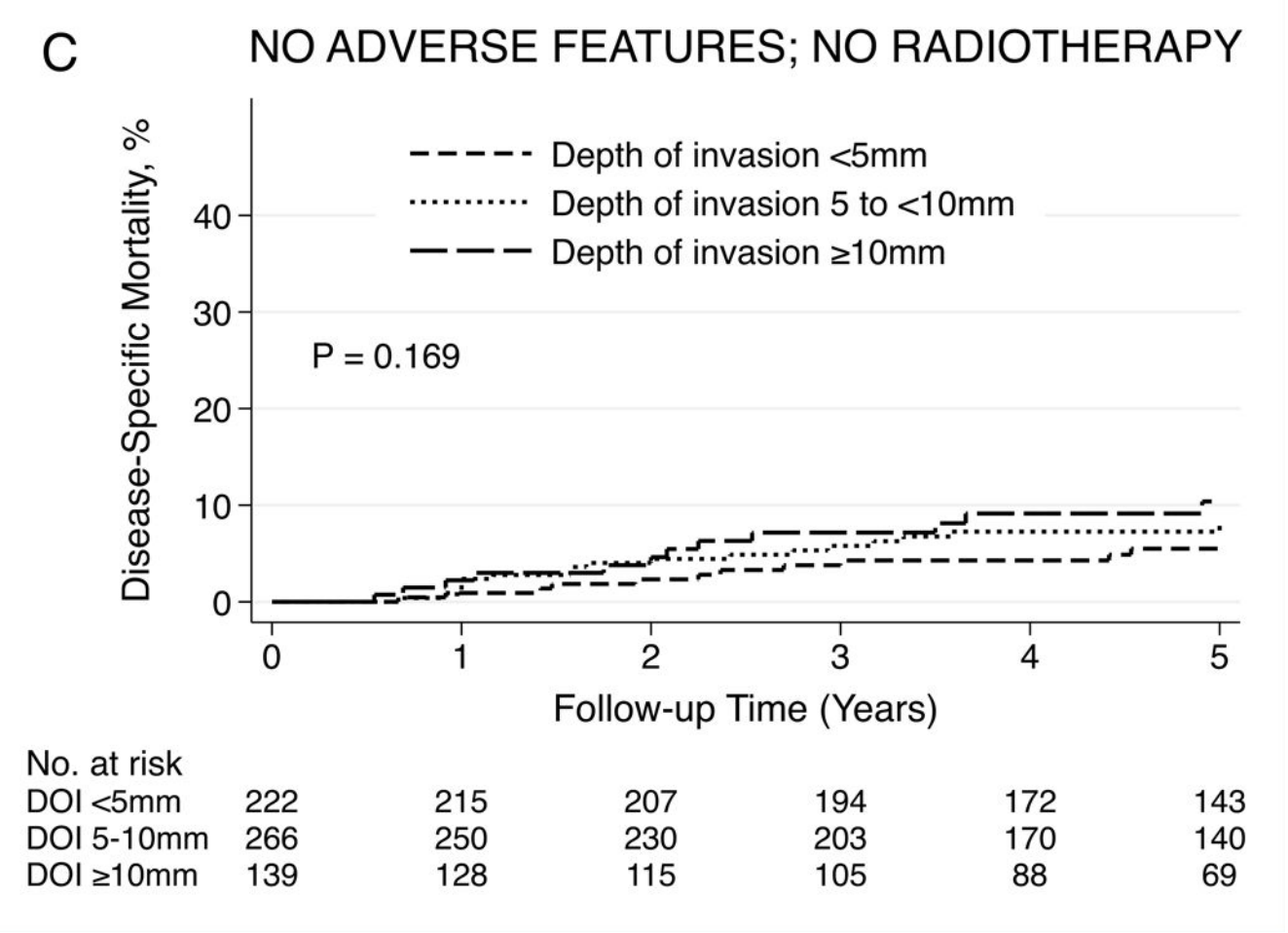


Figure 1.

Kaplan-Meier plots with risk tables of the entire study cohort demonstrating association between depth of invasion and (A) cumulative disease-specific mortality, (B) cumulative locoregional failure. Abbreviations: DOI, depth of invasion. Note that 10 patients were missing data necessary for calculation of disease-specific mortality and 7 for locoregional failure.







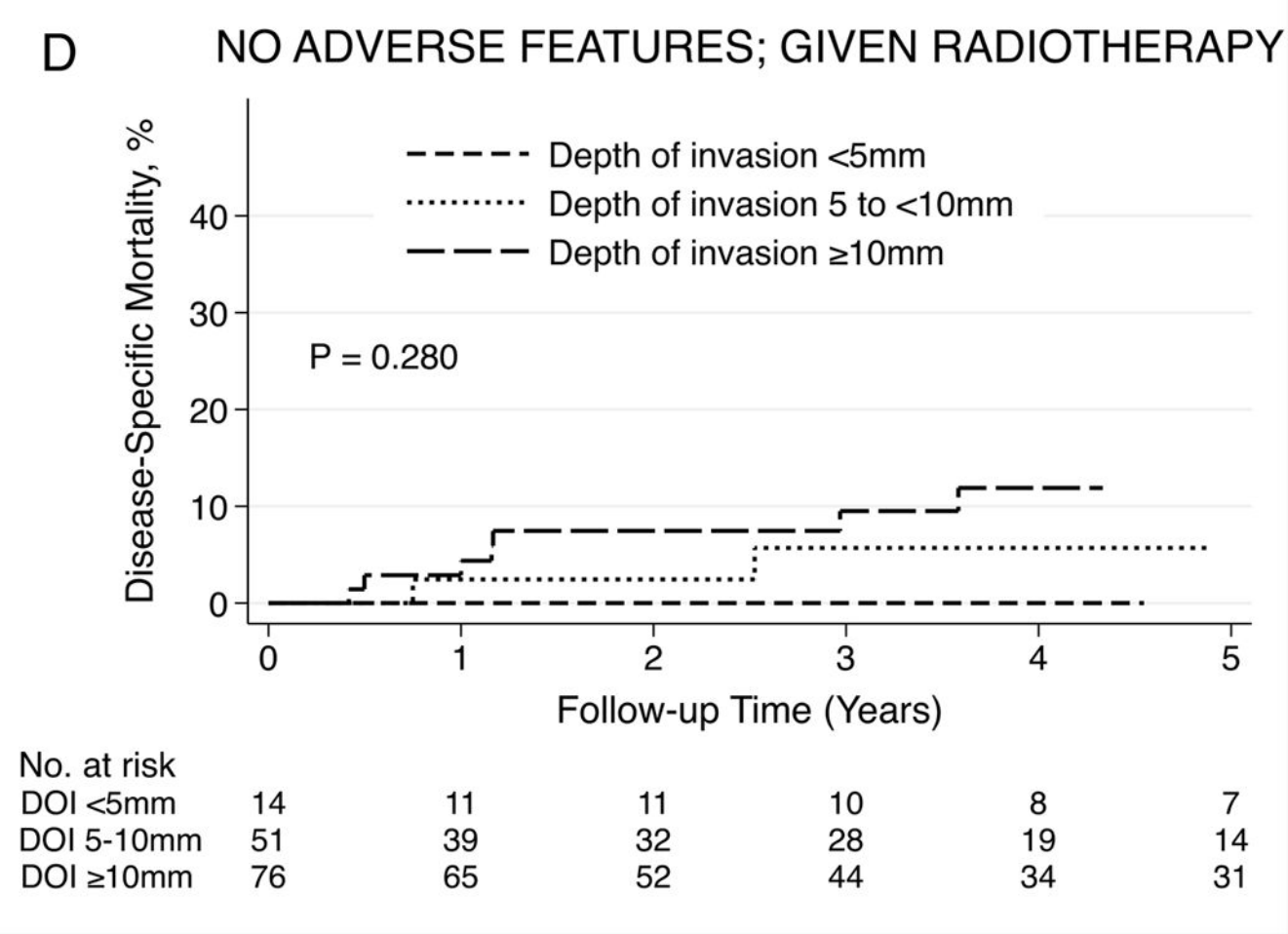
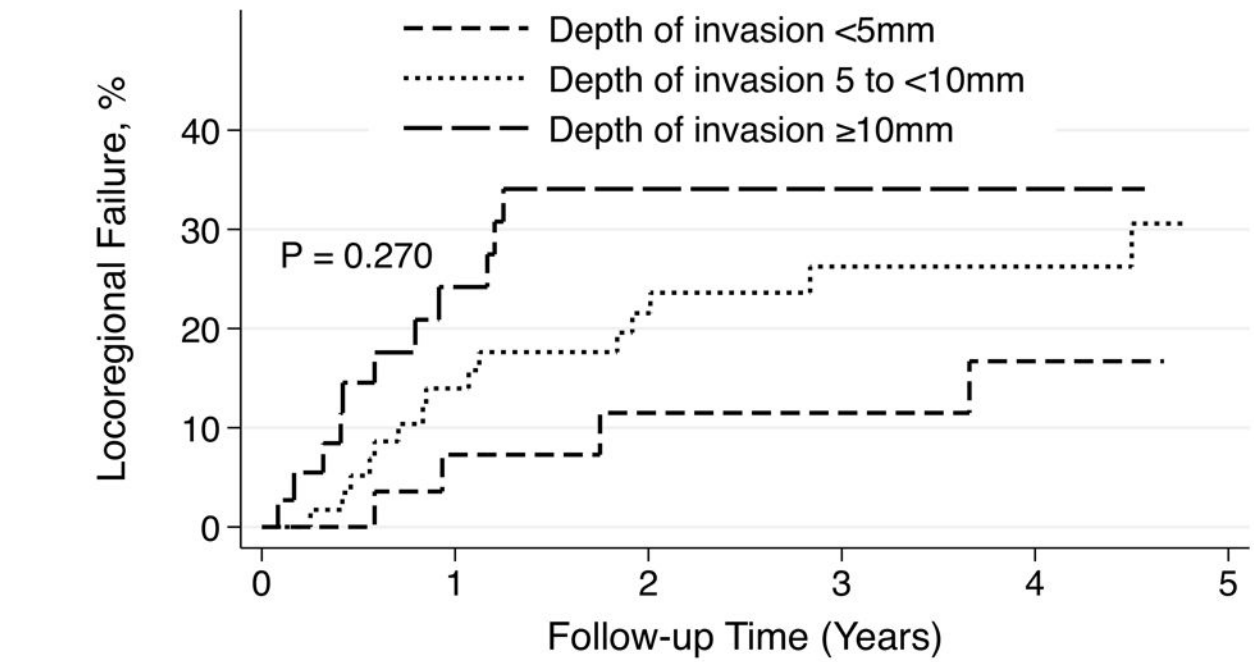
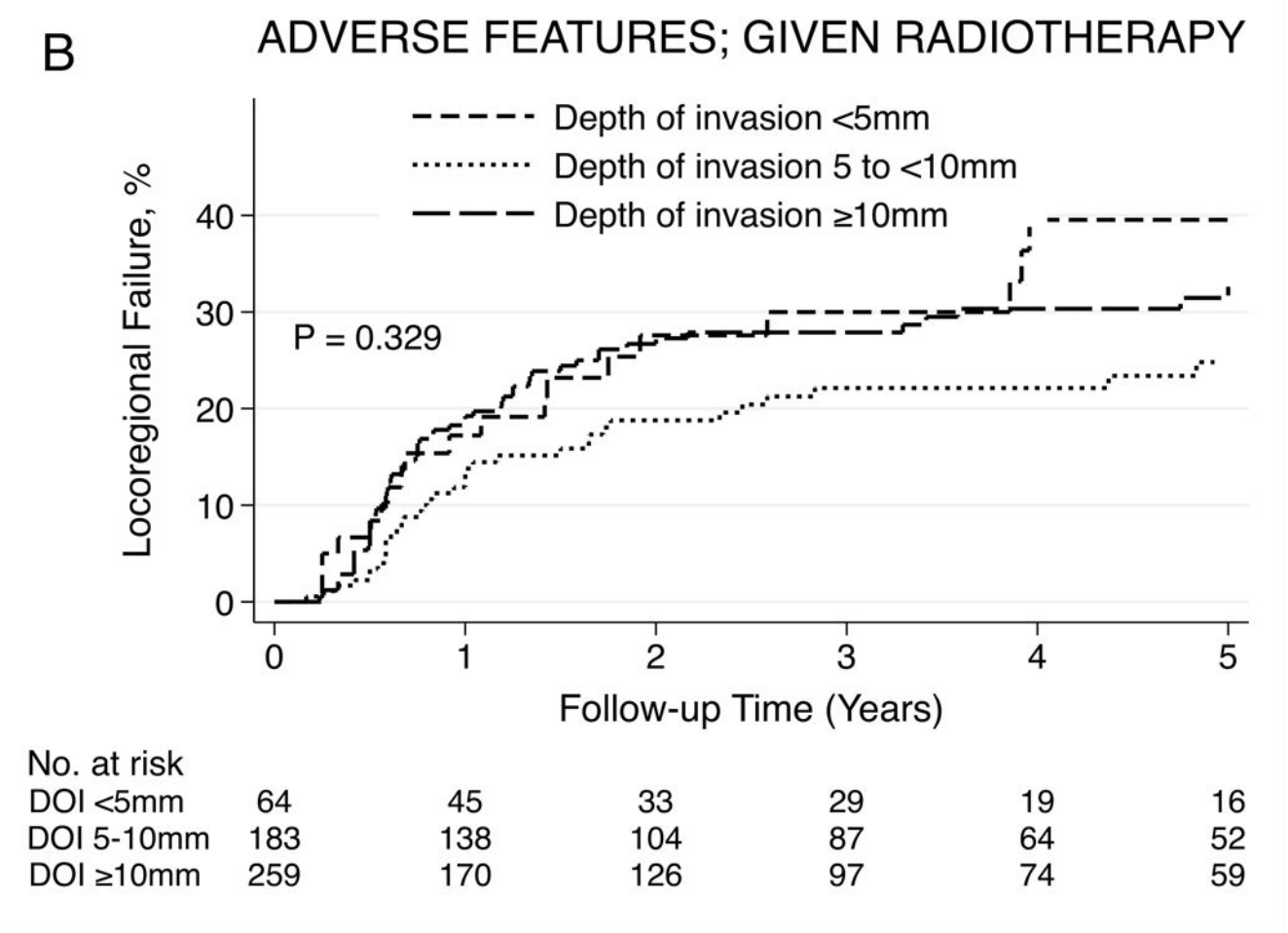


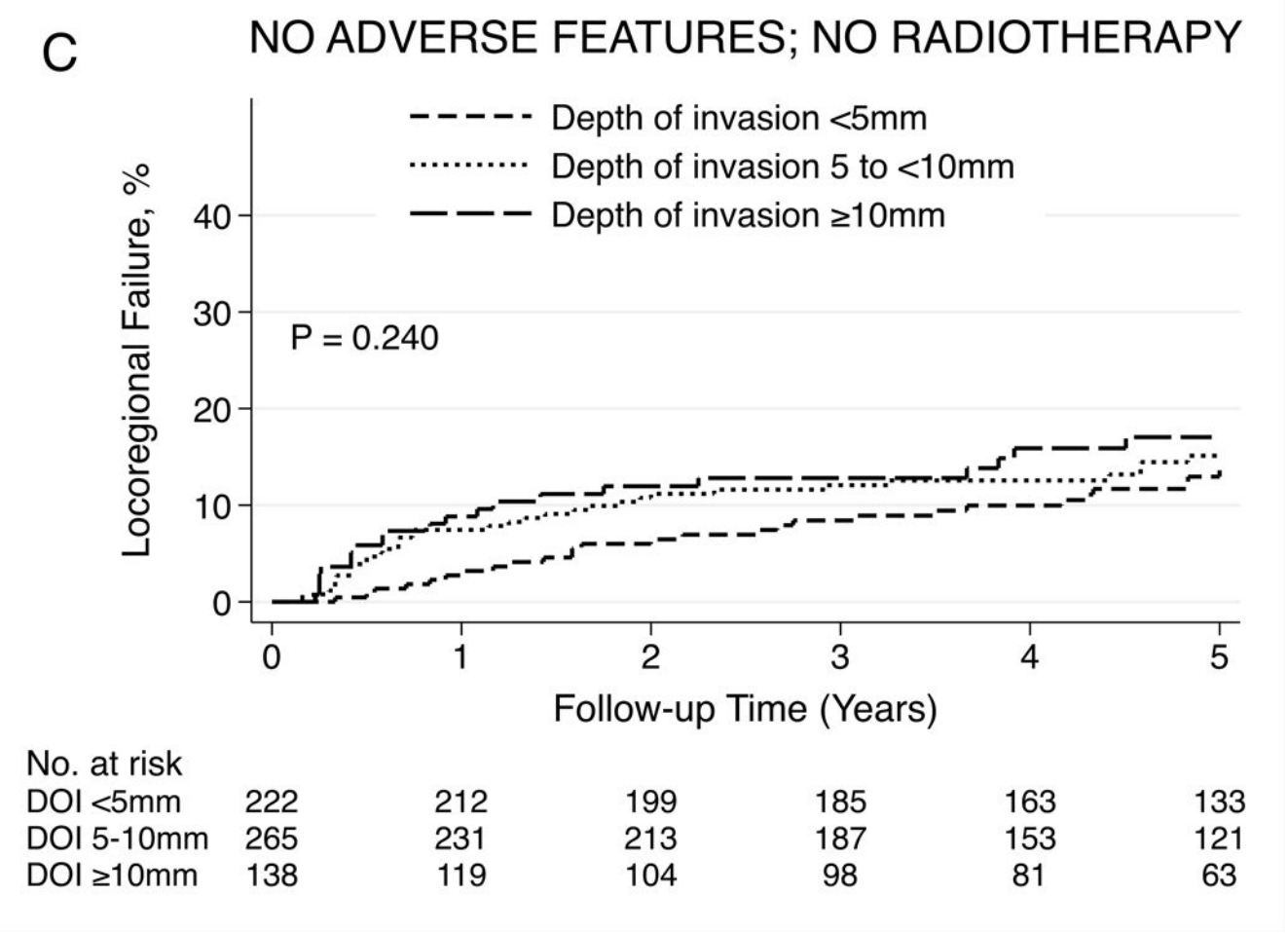
Figure 2.

Kaplan-Meier plots with risk tables demonstrating association between depth of invasion and cumulative disease-specific mortality within (A) the subgroup with at least one adverse feature (defined as one or more of: surgical margins <5mm; pathologically node positive disease) not receiving PORT, (B) the subgroup with at least one adverse feature that received PORT, (C) the subgroup with no adverse features which did not receive PORT, and (D) the subgroup with no adverse features which did receive PORT. Abbreviations: DOI, depth of invasion



No. at risk						
DOI <5mm	31	25	20	19	14	10
DOI 5-10mm	60	48	39	28	17	14
DOI ≥10mm	39	23	12	10	8	7





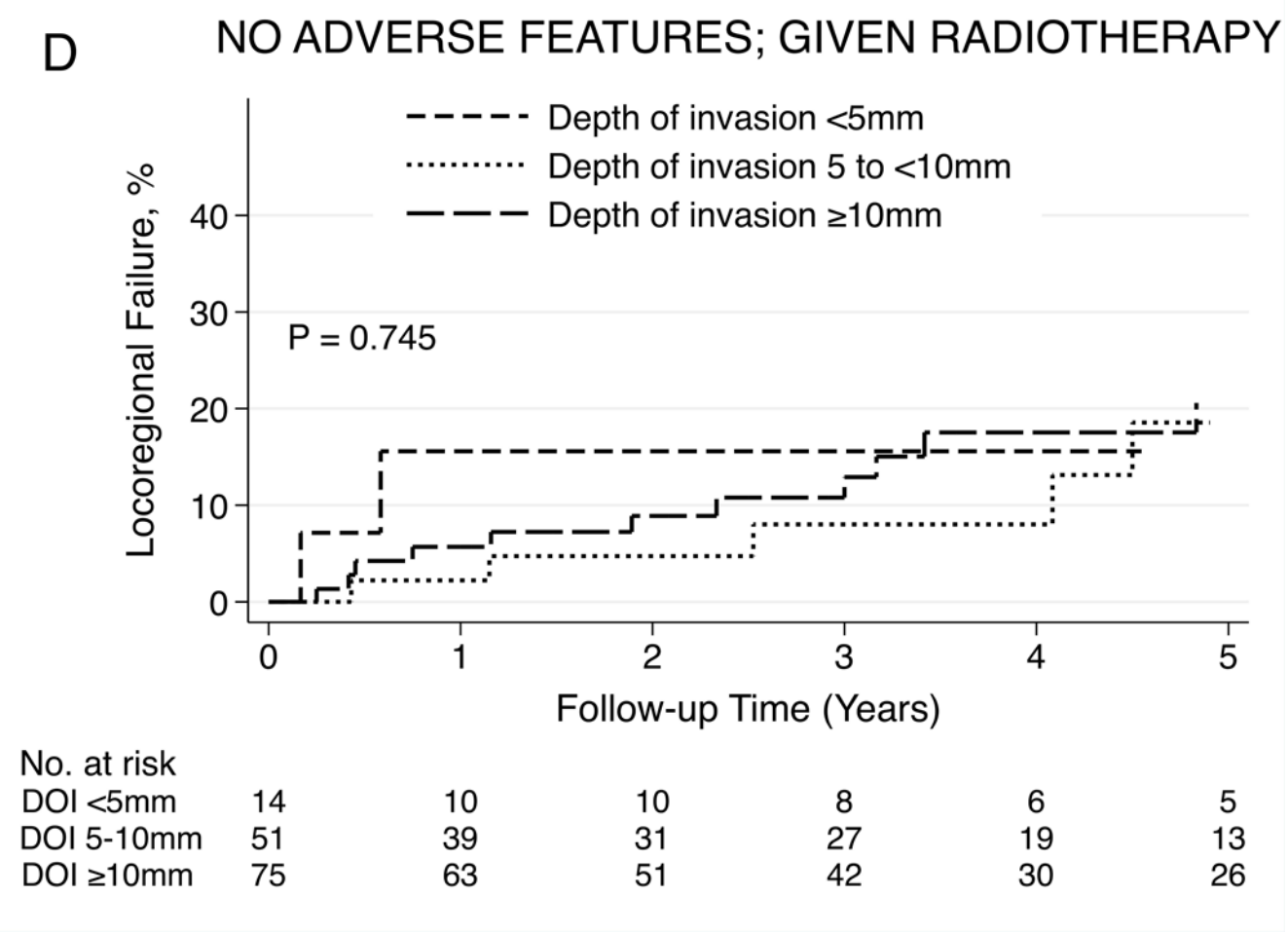


Figure 3.

Kaplan-Meier plots with risk tables demonstrating association between depth of invasion and cumulative locoregional failure within (A) the subgroup with at least one adverse feature (defined as one or more of: margins <5mm; pathologically node positive disease) not receiving PORT, (B) the subgroup with at least one adverse feature which received PORT, (C) the subgroup with no adverse features which did not receive PORT, and (D) the subgroup with no adverse features which did receive PORT. Abbreviations: DOI, depth of invasion

Table 1.

Patient clinicopathological data

Variable	No. of patients	%
Age, years		
≤45	366	26.0
46 to 55	383	27.2
56 to 65	345	24.5
≥66	315	22.4
Sex		
Male	1065	75.6
Female	344	24.4
Primary tumor size		
≤2 cm	454	32.2
>2–4 cm	955	67.8
Pathological N category *		
N0	918	65.2
N1	201	14.3
N2	288	20.4
N3	2	0.1
Extracapsular nodal spread		
Absent	1186	84.2
Present	213	15.1
Unknown	10	0.7
Surgical excision margin		
Clear	1146	81.3
Close (<5mm)	210	14.9
Involved	52	3.7
Unknown	1	0.1
Adjuvant therapy		
No	697	49.5
Radiotherapy	468	33.2
Radiotherapy + cisplatin	193	13.7
Radiotherapy + cetuximab	50	3.5
Unknown	1	0.1
Decade of primary treatment		
1990–1999	316	22.4
2000–2011	1093	77.6
Study center		
Brescia, Italy	16	1.1
São Paulo, Brazil	128	9.1
Petach Tikva, Israel	45	3.2
SHNCI, Australia	121	8.6

Variable	No. of patients	%
Camargo, São Paulo, Brazil	33	2.3
Cologne, Germany	138	9.8
MSKCC, USA	115	8.2
Southern Illinois, USA	20	1.4
CGMH-Taoyuan, Taiwan	684	48.6
Tel Aviv, Israel	56	4.0
Tata Memorial Hospital, India	53	3.8

* Based on the 7th edition American Joint Committee on Cancer Staging Manual

Abbreviations: SHNCI, Sydney Head & Neck Cancer Institute; MSKCC, Memorial Sloan-Kettering Cancer Center.

Table 2.

Correlation between depth of invasion and other adverse pathologic features

Variable	Depth of invasion, mm No. of patients (%)			*p* value
	<5	5 to <10	≥10	
Primary tumor size				
≤2 cm	175 (52.9)	211 (37.5)	68 (13.2)	<0.001
>2–4 cm	156 (47.1)	352 (62.5)	447 (86.8)	
Pathological N category *				
N0	265 (80.1)	374 (66.4)	279 (54.2)	<0.001
N1	34 (10.3)	84 (14.9)	83 (16.1)	
N2	32 (9.7)	103 (18.3)	153 (29.7)	
N3	0 (0)	2 (0.4)	0 (0)	
Extracapsular nodal spread				
Absent	298 (90.0)	477 (85.8)	411 (80.3)	<0.001
Present	33 (10.0)	79 (14.2)	101 (19.7)	
Surgical excision margin				
Clear	289 (87.3)	468 (83.3)	389 (75.5)	<0.001
Close (<5mm)	38 (11.5)	75 (13.4)	97 (18.8)	
Involved	4 (1.2)	19 (3.4)	29 (5.6)	

*Based on the 7th edition American Joint Committee on Cancer Staging Manual

Table 3.

Univariate and multivariate analyses of the association between depth of invasion with disease-specific survival and locoregional control

	Disease-Specific Survival		Locoregional Control	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Univariate Analyses				
Categorical depth (mm)				
≤5	Referent		Referent	
5 to <10	1.66 (1.05−2.62)	0.030	1.27 (0.91−1.76)	0.156
≥10	3.28 (2.11−5.08)	<0.001	1.63 (1.18−2.25)	0.003
Continuous depth (mm) *	1.90 (1.51−2.40)	<0.001	1.38 (1.16−1.64)	<0.001
Multivariate Analyses †				
Categorical depth (mm)				
≤5	Referent		Referent	
5 to <10	1.30 (0.82−2.07)	0.267	1.10 (0.78−1.53)	0.595
≥10	2.02 (1.27−3.21)	0.003	1.31 (0.92−1.88)	0.135
Continuous depth (mm) *	1.43 (1.10−1.84)	0.006	1.23 (1.01−1.50)	0.041

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Depth of invasion was analyzed as a continuous variable after logarithmic transformation.

† Multivariate analyses performed with multivariate Cox regression models stratified by study center and adjusting for age in years, primary tumor size (≤2cm versus >2–4cm), pathological N stage (N0, N1, N2, N3), surgical margin status (clear, close [<5mm], involved), extracapsular nodal spread (absent, present), time period of primary treatment (1990–1999, 2000–2011), and adjuvant radiotherapy.