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## **The budding and depth of invasion model in oral cancer – a systematic review and meta-analysis**

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ABSTRACT

**Background:** Tumour budding (B) and depth of invasion (D) have both been reported as promising prognostic markers in oral squamous cell carcinoma (OSCC). This meta-analysis assessed the prognostic value of the tumour budding and depth of invasion combination (BD model) in OSCC.

**Methods:** Databases including OvidMedline, PubMed, Scopus, and Web of Science were searched for articles that studied the BD model as a prognosticator in OSCC. PICO search strategy was “In OSCC patients, does BD model have a prognostic power?” We used the reporting recommendations for tumour marker prognostic studies (REMARK) criteria to evaluate the quality of studies eligible for systematic review and meta-analysis.

**Results:** Nine studies were relevant as they analysed the BD model for prognostication of OSCC. These studies used either haematoxylin and eosin (HE) or Pan-Cytokeratin (PCK) stained resected sections of OSCC. Our meta-analysis showed a significant association of BD model with OSCC disease free survival (hazard ratio = 2.02; 95% confidence interval = 1.44 - 2.85).

**Conclusions:** The BD model is a simple and reliable prognostic indicator for OSCC. Evaluation of the BD model from HE- or PCK-stained sections could facilitate individualized treatment planning for OSCC patients.

**Keywords:** oral squamous cell carcinoma, tumour budding, depth of invasion, BD model, prognostication, survival analysis.

## **Introduction**

Globally, oral squamous cell carcinoma (OSCC) constitutes 4.7% to 20.3% of all head and neck malignancies (Chen *et al.* 2016; Siegel, Miller, & Jemal, 2017) and has less than 50% 5-year overall survival rate (Kim *et al.* 2016). Patients with recurrent OSCC have reduced survival rates even with early-stage disease, as 20% to 40% of the patients have occult cervical lymph node metastasis (Bittar, Ferraro, Ribas, & Lehn, 2016; Safi *et al.* 2017).

Treatment planning in OSCC is usually based on the cTNM classification and tumour histological grade (El-Naggar, Chan, Grandis, Takata, & Slotweg, 2017). However, several studies have highlighted shortcomings of the WHO histologic grade classification in predicting the prognosis of OSCC patients (Almangush *et al.* 2015; Brierley, Gospodarowicz, & Wittekind, 2017; Müller, 2017). In addition, disease progression and treatment response still differ conspicuously among patients with a similar cTNM stage (Lindenblatt *et al.* 2012; Low, Gao, Elliott, & Clark, 2015; Sawazaki-Calone *et al.* 2015). Therefore, it is crucial to identify more credible prognostic models based on histological features of the tumour to develop more appropriate treatment plans for OSCC patients. Almangush and colleagues first introduced the prognostic BD score for OSCC, which consists of the histological parameters tumour budding (B) and depth of invasion (D), (Almangush *et al.* 2015).

Tumour budding is defined as fewer than five cancer cells forming a cell cluster(s) at the invasive front of the tumour (Kadota *et al.* 2015; Rogers *et al.* 2016). Tumour budding has been shown to correlate with epithelial to mesenchymal transition (EMT) in many carcinomas, including tongue cancer (Wang *et al.* 2011; Liang *et al.* 2013). In addition, tumour budding is a risk factor for a late neck recurrence (Hori *et al.* 2017). Depth of invasion (D) is defined as a measurement from the basement membrane zone to the deepest point of cancer cell invasion (Berdugo *et al.* 2019). In the recent 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) classification, Depth of invasion has been added into the TNM staging of the tumour to improve its prognostic value (Amin *et al.* 2017).

Many studies have reported on the prognostic value of the BD model in cancers from different subsites of the oral cavity (Almangush *et al.* 2015; Sawazaki-Calone *et al.* 2015; Seki *et al.* 2016; Strieder *et al.* 2017; Hori *et al.* 2017; Yu *et al.* 2019). These publications highlighted the future prospect of considering BD scores in treatment planning of OSCC. Our hypothesis was to validate through pooled analyses of the published studies whether BD model has a significant prognostic value in OSCC. Therefore, this study aimed to systematically review the literature to retrieve all publications related to the BD model in OSCC and to conduct a meta-analysis of the eligible studies.

## Methods

**Search Protocol:** Two independent reviewers A.W and O.O conducted the systematic review.

The databases of OvidMedline, PubMed, Scopus, and Web of Science were searched using the following keywords: ('oral' or 'mouth' or 'tongue' or 'floor of mouth' or 'lip' or 'gingiva' or 'buccal' or 'palate') AND ('cancer' OR 'carcinoma' OR 'neoplasm' OR 'tumor' OR 'tumour') AND ('bd' OR 'bd model' OR 'budding and depth' OR 'budding and depth of invasion'). The PICO question was formulated as follows: "In OSCC patients, does BD model have a prognostic power?"

Studies in English language that evaluated BD model in cohorts of OSCCs were included in our systematic review. Studies in other languages or studies which did not present BD model analysis in OSCC were excluded. References of all relevant articles were also manually searched to ensure inclusion of all eligible studies. Studies on animal samples, and conference abstracts were also excluded. The end point of the search was February 2020. RefWorks software was used to manage records and the data.

**Combination of tumour budding (B) and depth of invasion (D):** The BD model is originally based on the following three scores: 0, 1, and 2 (Almangush *et al.* 2015). A tumour with a depth of invasion < 4 mm and fewer than five buds of carcinoma cells at the invasive front is considered low risk and scored '0'. A tumour with depth of invasion  $\geq$  4 mm and with fewer than five buds at the invasive front, or a superficial tumour with < 4 mm depth of invasion but with five or more buds at the invasive front is considered at intermediate risk and scored '1'. A tumour with depth of invasion  $\geq$  4 mm and with five or more buds is considered high risk and scored '2' (Figure 1. Copyright (2016) Wiley. Used with permission from Strieder *et al.* Comparative analysis of three histologic grading methods for squamous cell carcinoma of the lip, *Oral Diseases*, John Wiley and Sons).

**Quality Assessment:** The reporting recommendations for tumour marker prognostic studies (REMARK) guidelines (Altman, McShane, Sauerbrei, & Taube, 2012) were followed to assess the quality of studies that evaluated the prognostic value of the BD model in OSCC. The guidelines for systematic review and meta-analysis of prognostic factor studies were followed (Riley *et al.* 2019)

along with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P), (Moher *et al.* 2015).

**Statistical Methods:** The statistical software R (version 3.4.0) was used to run the ‘meta’ package (version 4.8-1) for meta-analysis. For each analysis, both an inverse variance weighted fixed effect analysis was performed. The random effect model analysis was considered as the main result to account for possible heterogeneity among studies (Higgins & Thompson, 2002). In addition to meta-analysed effect sizes, we also included the estimated proportion of variation in effect sizes due to heterogeneity ( $I^2$ ).

## Results

**Search Results:** A total of 396 hits were retrieved from databases. There were 116 duplicates that were deleted and 280 studies were included for further analyses (Figure 2). Out of these, nine studies related to the BD model in OSCC were included in this systematic review. Among these, three studies were from Japan, one from Finland, two had cases from both Finland and Brazil, two were from Brazil, and one was from China. In Table 1, each study is reported with the total number of cases, TNM stage, oral subsite, primary treatment, follow-up time, staining method/s used, cut-off point for budding and depth of invasion, survival or sensitivity and specificity analyses, hazard ratio (HR), and P value.

### **Meta-analysis of disease-free survival:**

Only four studies reported detailed statistical analyses for disease-free survival (DFS), including HRs and 95% confidence intervals (CI); these studies were included in the meta-analysis visualized using forest plots (Figure 3, a and b).

The first forest plot (Figure 3a) included all multivariate results of BD as the predictor of interest and DFS as the response variable (HR = 2.02, 95% CI = 1.44 - 2.85). In the second forest plot (Figure 3b), both multivariate and univariate analyses that reported HR values for BD as the predictor and DFS as the response variable were combined to attain cumulative effect size (HR = 1.82, 95% CI = 1.44 -

2.29). The results of the meta-analysis did not present any heterogeneity ( $I^2 = 0$ ). Funnel plots were employed to evaluate bias across studies with HR as the effect estimate and standard error as the measure of precision. In the funnel plots (Figure 4, a and b), the effect estimates were within the expected 95% region marked by the diagonal segments and neither funnel plot indicated a bias.

#### **Association of the BD model with disease-specific survival and overall survival:**

Although the published results (Table 1) on the association of BD model with disease-specific survival (DSS) and overall survival (OS) were not enough to conduct meta-analyses, there was some evidence indicating a promising prognostic value for the BD model in prediction of these two survival outcomes. For example, Almangush et al. (2015) revealed a significant association of the BD model with DSS of OTSCC patients (HR = 5.11, 95% CI 2.05 - 12.75;  $P < 0.001$ ). In contrast to other parameters WHO grading system, histological risk (HR) model and malignancy grading of the deep invasive margins (MG), only the BD model correlated with DSS ( $P = 0.009$ ) in a study by Sawazaki-Calone et al. (2015). Overall survival (OS) is significantly associated with both budding and tumour depth of invasion ( $P < 0.05$ ) in Seki et al. (2016). These results were similar to those observed by Strieder et al. (2017), where OS was also associated with the BD model ( $P = 0.045$ ). Similarly, Yu et al. (2019) demonstrated that BD score associated with OS (HR = 2.77, 95% CI 1.78 - 4.33;  $P < 0.001$ ).

#### **Association of the BD model with clinicopathological factors:**

A significant association ( $P < 0.001$ ) of the BD model with histological risk (HR) model was demonstrated by Sawazaki-Calone et al. (2015) and Seki et al. (2016), who reported 100% sensitivity for tumour budding ( $>3$ ) and tumour depth of invasion ( $>3$  mm) for neck metastasis (Seki, Sano, Yokoo, & Oyama, 2016). A strong association was also reported between neck recurrence and the BD model with 89% sensitivity and 95% specificity by Hori et al. (2017). A recent publication (Hori *et al.* 2020) revealed an association between neck recurrence and the BD model (HR = 5.46, 95% CI 1.08 - 27.52;  $P < 0.05$ ). Yu *et al.* (2019) observed that T-stage ( $P = 0.002$ ), lymph node metastasis ( $P < 0.001$ ), clinical stage ( $P < 0.001$ ), invasive pattern ( $P < 0.001$ ), Glasgow Microenvironment Score



(GMS) ( $P = 0.031$ ), and tumour-to-stroma percentage ( $P = 0.006$ ) were all associated significantly with BD scores.

## Discussion

This study aimed to meta-analyse the prognostic significance of BD model in studies of OSCC. It was hypothesized that BD model has a prognostic role in OSCC. For this purpose, databases were searched to gather studies of BD model for a systematic review and meta-analysis.

The recent WHO classification of head and neck tumours pointed out that the conventional histological grading (well, moderate, or poorly differentiated OSCC) correlates poorly with clinical outcome and a non-cohesive pattern of invasion, perineural and lymphovascular invasion, bone invasion, and tumour thickness of  $\geq 4$  mm is associated with poorer prognosis (El-Naggar *et al.* 2017). The histological grading system is easier to analyse and is therefore still widely used in clinical pathology reports. However, this system has been widely criticized by several authors (Müller, 2017; Brierley *et al.* 2017). Here, our meta-analysis revealed that readily available BD score is significantly associated with DFS as an independent prognostic indicator. Additionally, in many studies a number of clinicopathological factors (such as T-stage, lymph node metastasis, clinical stage, invasive pattern) and both of OS and DSS of OSCC patients were significantly associated with the BD model.

In our systematic review, all the studies used surgery as primary treatment. Some studies presented significant results of the BD model for OSCC in OS: (HR = 2.77, 95% CI 1.78 - 4.33;  $P < 0.001$ ), (Yu *et al.* 2019), and DSS: (HR= 5.11, 95% CI 2.05-12.75;  $P < 0.001$ ) (Almangush *et al.* 2015; Yu *et al.* 2019). Specificity of 93% and 96.9% for BD model was presented by Hori *et al.* (2017) and Almangush *et al.* (2018) respectively. However, the published studies were insufficient to conduct meta-analyses on OS or DSS. Four original studies had appropriate statistics for meta-analyses of DFS. To avoid bias due to potential heterogeneity, a random-effect model (in addition to a fixed-effect model) was employed to combine heterogenous studies (Guolo & Varin, 2015). However, as we did not detect any heterogeneity, therefore the random-effect model produced the same results as the fixed-effect model. We conducted two meta-analyses (Fig. 3), one with HR values from the three

multivariate analyses for DFS (Almangush *et al.* 2015; Sawazaki-Calone *et al.* 2015; Hori *et al.* 2020) (Fig. 3a), and the other that also included one additional study (Yu *et al.* 2019) that provided only univariate analysis results for DFS (Fig. 3b). Both forest plots indicated significant meta-analysed HR values and thus validated the results of the studies that presented prognostic results of the BD model in DFS of OSCC patients. Based on these analyses, the BD model was shown to be a prognostic indicator for DFS in OSCC, which was consistent across these studies. Of note, tongue was the oral subsite in most of the included studies. However, inclusion of different subsites along with different stages in the meta-analysis were reported and are among the limitations. Despite these shortcomings, the gathered evidence was sufficient to propose that a high BD score is an indicator for poor prognosis in OSCC.

In the literature, tumour budding has been analysed in at least 10 studies of OSCC (Jensen *et al.* 2015; Angadi *et al.* 2015; Almangush *et al.* 2015; Manjula, Augustine, Selvam, & Mohan, 2015; Xie *et al.* 2015; Seki *et al.* 2016; Boxberg *et al.* 2017; Pedersen *et al.* 2017; Hori *et al.* 2017; Arora *et al.* 2017). The cut-off point of five buds was advocated in most of these studies, and only one group (Seki *et al.* 2016) adjusted the cut-off point of three buds. Budding represents two malignant features, namely discohesion of cells and active invasion. Therefore, tumour budding has been considered as characteristic behaviour of an aggressive tumour (Wang *et al.* 2011). Recently, a study presented tumour budding and worst pattern of invasion to be an important risk factors to predict lymph node metastasis in all stages of OSCC (Chatterjee *et al.*, 2019). Outside the oral cavity, tumour budding is associated with poor prognosis in several other malignancies, such as bladder, cervical, rectal, breast, cutaneous, and hepatocellular cancers (Fukumoto *et al.* 2016; Huang, Cai, Xu, Guo, & Wang, 2016; Jäger *et al.* 2018; Lino-Silva, Salcedo-Hernández, & Gamboa-Domínguez, 2018; Voutsadakis, 2018; Wei *et al.* 2020).

Depth of invasion has predictive value for lymph node metastasis and loco-regional recurrence in OSCC (Shinn *et al.* 2018). In our review, six of the studies set a cut-off point of 4 mm (Sawazaki-Calone *et al.* 2015; Almangush *et al.* 2015; Strieder *et al.* 2017; Almangush *et al.* 2018a; Almangush *et al.* 2018b; Yu *et al.* 2019), and in three Japanese studies (Seki *et al.* 2016; Hori *et al.* 2017, 2020) the cut-off point for depth of invasion was adjusted at 3 mm. The latest cancer staging

manual of the AJCC (8<sup>th</sup> edition) considers depth of invasion in the TNM classification system (Amin *et al.* 2017). This addition into the TNM classification already improves the predictive value and stratification of different TNM stages, including recognition of low-risk patients with a reduced survival rate (Rodrigues *et al.* 2020).

The BD score is relatively simple for objective analysis (Sawazaki-Calone *et al.* 2015) and as it is possible to evaluate even from the originally HE-stained slides, the analyses are inexpensive and the score can easily be added to clinical pathology reports. In contrast, the other histological models, such as malignancy grading of the deep invasive margins (MG), (Bryne, Koppang, Lilleng, & Kjaerheim, 1992) and histological risk (HR) model (Brandwein-Gensler *et al.* 2005) are more difficult to apply (Bundgaard *et al.* 2002; Gueiros, Coletta, Kowalski, & Lopes, 2011; Lindenblatt *et al.* 2012). To the best of our knowledge, this is the first systematic review and meta-analysis on the prognostic value of BD model in OSCC.

## Conclusion

In this systematic review, we found a total of nine studies that all presented significance of BD model as a prognosticator in OSCC. Based on the current meta-analysis, we here conclude that the BD model has a strong prognostic power for DFS in OSCC patients. In the future, other practical histopathological models, such as tumour-to-stroma ratio and tumour infiltration lymphocytes, combined with BD score, should be tested to possibly upgrade the prognostic power of histopathological features in OSCC.

## Figure Legends

**Figure 1:** Budding and Depth of invasion model: (a) Buds or islands of tumour invasion with < 5 cells (100  $\mu$ m). (b) Length of the tumour area with greatest depth of invasion  $\geq$  4 mm.

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**Figure 2:** Flow diagram outlining the search strategy and the search results along various steps.

**Figure 3:** Forest plots for the pooled analyses of the studies that evaluated the prognostic value of the BD model in assessing DFS of OSCC. (a) All multivariate studies. (b) Multivariate and univariate results combined to obtain the cumulative result of meta-analysis.

(Few confidence limits are marginally different from the original values due to the rounding of hazard ratios and confidence limits to two digits).

**Figure 4:** Funnel plots constructed to assess overall effect. (a) All multivariate studies (b) All multivariate studies and one univariate study.

### **Authors contribution**

A.W designed the project, carried out the systematic review, run the meta-analysis, interpreted results, and wrote the manuscript. O.O carried out the systematic review, validated the systematic review, interpreted results, and wrote the manuscript. M.P run the meta-analysis, evaluated, interpreted, validated the meta-analysis, and wrote the manuscript. A.A designed the project, validated the systematic review, validated the meta-analysis, interpreted results, wrote the manuscript, and supervised the project. T.S designed the project, validated the systematic review, validated the meta-analysis, interpreted results, wrote the manuscript, and supervised the project.

### **References**

**Table 1: Summary of studies that examined the prognostic value of BD model in OSCC**

Authors, year (Country)	No. of cases	TNM stage	Oral subsite	Primary treatment	Follow-up	Staining method	Cutoff for budding	Cutoff for depth	Survival Analysis/ Sensitivity, Specificity	HR (95% CI)	P value	REMARK Quality of studies
Almangush <i>et al</i> , 2015 (Finland and Brazil)	311	T1-2N0	Tongue	Surgery	57 months	H-E	5 buds	4 mm	DSS	6.24 (2.59-15.04) <b>5.11 (2.05-12.75)</b>	< 0.001 <b>&lt; 0.001</b>	7
									DFS	2.14 (1.22-3.74) <b>2.19 (1.20-4.00)</b>	0.025 <b>0.033</b>	
Sawazaki-Calone <i>et al</i> , 2015 (Brazil)	113	T1-T4, N0, N+	Oral cavity	Surgery, surgery + postoperative RT, surgery + postoperative RT+CT	5 years	H-E	5 buds	4 mm	DSS	DSS in 5 yrs 32%	0.009	6
									DFS	<b>1.93 (1.23-3.00)</b> DFS in 5 yrs 49%	<b>0.003</b> 0.005	
									HRS		< 0.001	
Seki <i>et al</i> , 2016 (Japan)	91	T1-T4	Tongue and floor of mouth	Surgery, preoperative CT	4 months – 5 years	IHC	>3 buds	>3 mm	OS	100% sensitivity	< 0.05	6
									DFS		<b>&lt; 0.05</b>	
									Sensitivity			

										> 3mm budding		
Strieder <i>et al</i> , 2017 (Brazil)	53	T1-T4, N0,N+	Lip	Surgery, surgery + RT	57.5 months (T1/T2), 159.4 months (T3/T4)	H-E	5 buds	4 mm	OS (5 years)	75% (high risk cases)	0.045	6
Hori <i>et al</i> , 2017 (Japan)	48	cT1/2 N0M0	Tongue	Surgery	71 months	H-E	5 buds	>3 mm	Sensitivity	89% Sensitivity		6
									Specificity	95% Specificity		
										80% PPV 97% NPV		
Almangush <i>et al</i> , 2018a. (Finland and Brazil)	224	T1- 2N0	Tongue	Surgery	NA	H-E	5 buds	4mm	DFS	<b>3.42 (1.71-6.82)</b> 2.82 (1.46-5.42)	<b>0.004</b> 0.014	8
									DSS	<b>11.63 (3.83-35.31)</b> 10.43 (3.51-31.01)	<b>&lt; 0.001</b> < 0.001	
Almangush <i>et al</i> , 2018b (Finland)	100	NA	Tongue	Surgery	NA	H-E	5 buds	4mm	Sensitivity	57.1% (95% CI 39.4 - 73.7%)	Chi- square test < 0.001	6
									Specificity	96.9% (95% CI 89.3- 99.6%)		
Yu <i>et al</i> , 2019 (China)	246	T1- T2/ T3-T4	Tongue	Surgery	60 months	H-E	5 buds	4 mm	OS	BD, 2.77 (1.78-4.33)	< 0.001	8
									DFS	BD, 1.66 (1.21-2.27)	0.002	

Hori <i>et al</i> , 2020 (Japan)	62	T1- 2N0	Tongue	Surgery	68 months	H-E and PCK	5 buds	>3 mm	DFS	<b>BD, 2.06 (0.64-6.57)</b>	0.22	7
									Lymph node recurrence	BD, 5.46 (1.08-27.52)	< 0.05	

**Notes:**

a- Values in bold are from multivariate analysis

b- Almagush *et al*, 2015 and Almagush *et al*, 2018a are overlapped

c- HR and CI reported by Almagush *et al*, 2018 were for combined score of tumour-stroma ratio and BD model

d- Hori *et al*, 2017 and Hori *et al*, 2020 are overlapped

**Abbreviations:**

BD: Budding and depth of invasion

CI: Confidence interval

CT: Chemotherapy

DFS: Disease-free survival

DSS: Disease-specific survival

H-E: Hematoxylin and eosin staining

HR: Hazard ratio

HRS: Histological risk score

iBD: Inflammatory response, Budding and invasion depth

IHC: Immunohistochemical staining with cytokeratin or pan-cytokeratin

NA: Not available

NPV: Negative predictive value

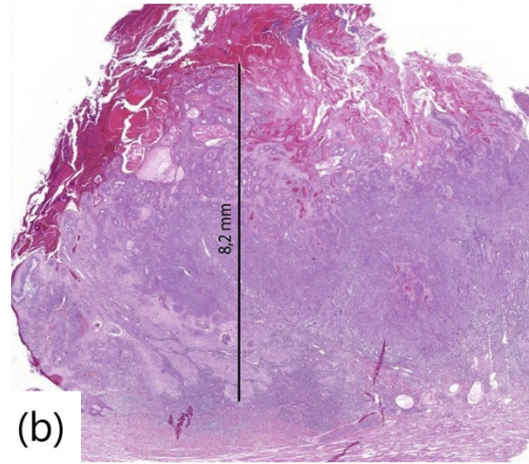
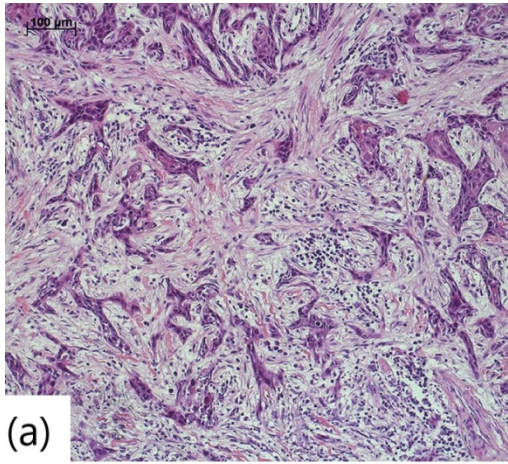
OS: Overall survival

PCK: Pan-Cytokeratin

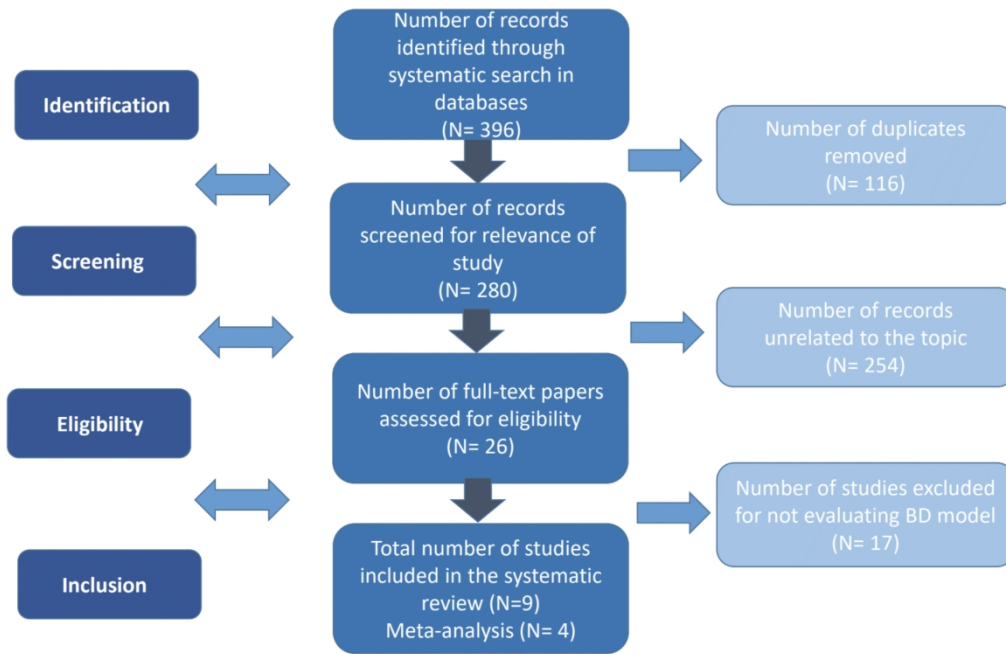
PPV: Positive predictive value

RT: Radiotherapy

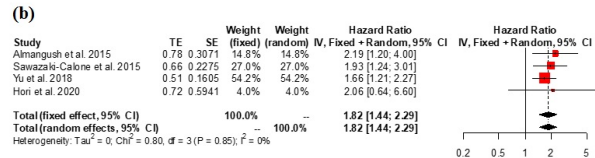
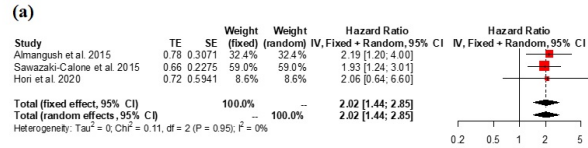




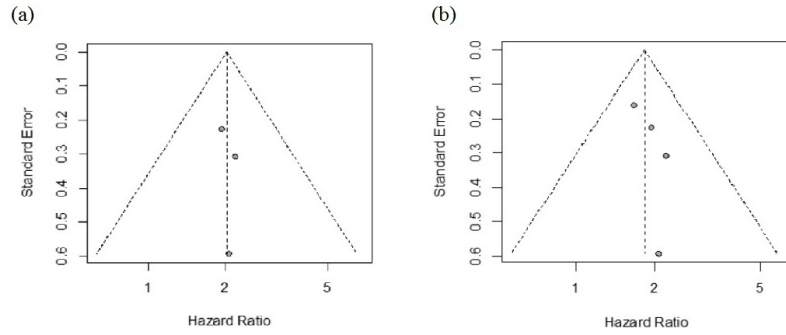
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