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Hyams Grading as a Predictor of Metastasis and Overall Survival in Esthesioneuroblastoma: A Meta-Analysis

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Abstract

Introduction: Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, represents up to 3% of all sinonasal neoplasms. Hyams histological grading can be a promising tool in predicting metastases and establishing prognoses for this complex tumor.

Methods: A systematic literature search was performed in PubMed, Ovid MEDLINE, and Cochrane databases. ENB patients with Hyams I-II or III-IV were categorized as low grade Hyams (LGH) or high grade Hyams (HGH), respectively. Binary and continuous random-effects models were applied to calculate Odds Ratios (OR) for the incidences of neck and distal metastases as well as for 5- and 10-year overall survival rates.

Results: Of the 57 screened articles published from 1993–2018, 16 (525 patients) and 21 (563 patients) provided data for tumor metastases and overall survival rates, respectively. Neck metastasis was observed in 18.2% of HGH *vs*. 7.9% of LGH patients. Distant metastasis was noted in 20.7% of HGH *vs*. 8.9% of LGH patients. LGH patients had 5- and 10-year overall survival rates of 81.2% and 64.0%, respectively, compared to 60.9% and 40.6%, respectively, for HGH patients. In comparing HGH *vs*. LGHs, collective OR for neck and distant metastases were 2.08 (95% CI 1.09–3.99; p=0.03) and 2.37 (95% CI 1.07–5.26; p=0.03), respectively. Moreover, in comparing LGH *vs*. HGHs, collective OR for 5- and 10-year overall survival rates were 3.39 (95% CI 2.09–5.49; p<0.001) and 3.03 (95% CI 1.82–5.06; p<0.001), respectively.

Conclusion: HGH ENBs, compared to LGH ENBs, are more likely to metastasize to neck or distal targets and to have lower overall survival rates.

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Keywords

Esthesioneuroblastoma; Olfactory neuroblastoma; metastasis; survival; meta-analysis

Introduction

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is a rare and malignant neuroectodermal tumor of the nasal cavity that was first described by Berger in 1924.[1] It represents up to 3–5% of sinonasal neoplasms and has been associated with metastatic tendency, though overall prognosis is often favorable compared to other sinonasal malignancies.[2–5] Previous uncertainties regarding the diagnosis and management of ENB can be attributed to its rarity in any single institution, varying biological activity and aggressiveness, susceptibility to misdiagnosis for other undifferentiated nasal cavity tumors, and the continuous evolution of treatment techniques.[4,6,7] However, multi-institutional efforts and large population- or systems-based databases are changing this.[8–11] Kadish and Dulguerov have proposed ENB classifications based on primary tumor extension and clinicoradiographic data, respectively.[6,12] The only grading system based on the histologic maturation and differentiation was developed by Hyams in 1988 which categorized ENBs from grades 1 to 4 from well to least differentiated.[13] However, the interpretation of this histopathological grading has not yet been fully established.

Hyams grading considers cellular architecture and pleomorphism, mitotic activity, and presence of necrosis, calcification, gland proliferation, and neurofibrillary matrix or rosettes.[2] It is common to binarize Hyams grading into low-grade Hyams (LGH; Hyams I-II) or high-grade Hyams (HGH; Hyams III-IV) to analyze tumor characteristics and prognoses.[14–17] While many studies have reported metastasis and survival of different Hyams-graded ENBs, an agreement on the relative risk or odds ratio in LGH *vs.* HGH has yet to be established. With an estimated 5-year survival of 65–73% for all ENBs,[7,18] a 2001 meta-analysis demonstrated that mean survival for LGH and HGH can be broken down to 56% and 25%, respectively.[7] Since histopathology is considered a potentially important prognostication,[16,17] there is need for a comprehensive evaluation of survival likeliness in LGH compared to HGH ENBs. Furthermore, there is evidence suggesting that regional and distant metastases rates are different based on Hyams grading. This can play a significant role in surveillance and treatment regimen.[11] We thus performed a comprehensive meta-analysis of all published articles to evaluate the odds ratio (OR) and strength of association of neck and distant metastasis as well as 5- and 10-year overall survival in LGH *vs.* HGH ENB patients.

Materials and methods

Institutional Review Board approval was deferred since only de-identified patient information accessible through the published literature was used. We performed a thorough literature search of the published articles in PubMed, Ovid MEDLINE, and Cochrane databases using “Hyams” and “esthesioneuroblastoma” or “olfactory neuroblastoma” keywords. Additionally, the included studies’ references were carefully assessed to ensure

complete inclusion of all scientific publications containing histopathologic data. Each article was independently evaluated by two authors (K.G. and A.A.) to be considered for inclusion. Study inclusion, data extraction, and analyses are in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[19] Our search criteria resulted in 57 studies published from March 1993 to March 2019. Case reports, reviews, and studies with unclear Hyams classifications or outcomes were excluded (Figure 1). Koch *et al.*[20] and Constantinidis *et al.*[21] utilized the same patient cohort, thus only the latter study, which was in English, was utilized here. Furthermore, Van Gompel had two studies in 2012 and 2013 with possibly overlapping patients, thus only the former study was utilized for survival data and the latter study was utilized for metastasis data.[22–23] Inclusion criteria mandated that studies report either of the outcome variables for both LGH and HGH tumors. Extracted data included patient demographics, Hyams classifications, eventual development and location of metastases, follow-up duration, and 5- and 10-year survival.

Overall survival was collected regardless of whether ENB was the cause of death. Some studies reported disease-free survival, but this was not analyzed due to the lower number of reports compared to overall survival. Neck metastasis was mostly indicated as metastasis “to the neck” or “cervical lymph node”, though it was sometimes deduced from reports of neck dissection. Distant metastasis locations consisted of dura, brain, breast, lung, and vertebrae; though, some were unspecified and simply reported as “distant” metastasis. We designated 5- and 10-year overall survival, as well as neck and distant metastasis, as primary outcome variables. These were compared between LGH and HGH ENBs using Review Manager v5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, 2014) via binary random-effects models for OR calculation. A p value < 0.05 was considered significant. Forest plots and the corresponding ORs and 95% confidence intervals (CI) were obtained for each outcome variable. Funnel plots were created to assess for potential study bias.

Results

Of the 57 screened articles published from 1993–2018, 16 (525 patients) and 21 (563 patients) studies provided data for tumor metastases and overall survival rates, respectively. Patient demographics and outcome variables of all studies used in analyzing tumor metastasis and overall survival rates are listed in Table 1 and Table 2, respectively. The metastasis data contained up to 303 LGH and 222 HGH subjects, whereas survival data included up to 349 LGH and 214 HGH patients. Overall neck and distant metastasis rates for all ENB patients were 12.4% and 13.9%, respectively. Neck metastasis was observed in 18.2% of HGH and 7.9% of LGH patients. Distant metastasis was noted in 20.7% of HGH and 8.9% of LGH patients. The sites of distant metastases consisted of brain or dura (n=29; 39.7%), spine or bone (n=16; 21.9%), lung (n=3; 4.1%), breast (n=2; 2.7%), liver (n=2; 2.7%), and unspecified (n=21; 28.8%). LGH patients had 5- and 10-year overall survival rates of 80.2% and 66.8%, respectively, compared to 54.2% and 35.6%, respectively, for HGH patients.

In comparing HGH *vs.* LGHs, collective OR for neck and distant metastases were 2.08 (95% CI 1.09–3.99; p=0.03) and 2.37 (95% CI 1.07–5.26; p=0.03), respectively (Figure 2). Moreover, in comparing LGH *vs.* HGHs, collective OR for 5- and 10-year overall survival

rates were 3.39 (95% CI 2.09–5.49; $p<0.001$) and 3.03 (95% CI 1.82–5.06; $p<0.001$), respectively (Figure 3). Funnel plots assessing studies' relative ORs showed nearly all studies falling within the 95% confidence boundaries (Figure 4).

Discussion

In this meta-analysis, we demonstrated that compared to LGH ENB, HGH ENB is associated with significantly higher rates of both neck and distant metastasis as well as lower rates of 5- and 10-year overall survival. Specifically, our ORs demonstrated that HGH ENBs were 2.1 and 2.4 times more likely to metastasize to the neck and distally, respectively. Also, LGH patients were 3.4 and 3.0 times more likely to have survived during the 5- and 10-year follow up, respectively. The difference in all four outcome variables was statistically significant between low and high Hyams grades. Therefore, we believe that the histopathologic features of a newly-diagnosed or under-surveillance ENB may continue to serve as an important tool in discussions regarding management, prognosis, and possible complications.

In the case of any tumor, early diagnosis is an important contributor to deciding management and improving prognosis. However, late diagnosis of ENB, possibly due to nonspecific symptoms resembling chronic rhinosinusitis or other more common sinonasal entities, can lead to poorer prognosis.[21,24] These indistinct symptoms can consist of unilateral nasal obstruction, loss of sense of smell, epistaxis, epiphora, and headache.[25,26] This combined with the rare annual incidence of 0.4 per million people[27] and variability in treatment response[15,28] has made ENB a difficult entity to study in any single institution. There is also a moderate to high probability of extraprimary recurrence after therapy, making long-term follow up an important component of management.[29,30] As a result, none of the main ENB classification systems has yet been deemed the gold standard for predicting metastasis or prognosis.

There exists a mix of studies that demonstrate either presence or absence of significant differences in survival based on Hyams grading.[15,21,30,31] In a 2001 meta-analysis, Dulguerov suggested that Hyams grading was a significant prognosis factor with mean survivals of 56% and 25% for LGH and HGH, respectively.[7] A 2014 population-based analysis of the largest ENB cohort revealed 84% LGH and 40% HGH for 5-year overall survival, and 67% LGH and 34% HGH for 10-year overall survival.[17] These studies agree with our findings which demonstrated a 5-year survival rate of 80% and 54% and a 10-year survival rate of 67% and 36% for LGH and HGH, respectively. In a 2010 review by Kane, Hyams grading was also a significant prognostic factor in the context of different treatment modalities including surgery, radiotherapy, chemotherapy, or a combination thereof.[16] Kane reported that in addition to Kadish grading and age, HGH was an independent predictor of poor survival with a 4.8 hazard ratio.[16] Our ORs corroborated this information, showing LGH ENB patients to be 3.0–3.4 times more likely to survive after 5 and 10 years as compared to HGH ENB.

Both cervical and distant metastasis appear to be common in ENB regardless of grading or time from diagnosis.[25] Neck metastasis and regional recurrence is reported in around 5%

−20% of ENB patients.[7,8,28,32,33] This is in accordance with our metastasis data showing 12–14% neck and distant metastasis. LGH ENB has been shown to be associated with local recurrence whereas HGH ENB can frequently involve higher T4 staging and brain metastasis.[34] Two large-cohort analyses by VanGompel and Ball have suggested that neck metastasis is a predictor of survival.[2,22] Accordingly, we displayed that HGH ENBs were more than twice likely to metastasize to both neck or distant targets, the same positive association as in the case of survival. Jiang and colleagues have argued for the efficacy of elective neck irradiation for ENB patients with clinically node-negative necks.[35] Others have advocated for elective radiation of the N0 neck in higher grade or stage ENB cases.[35–37] Hyams grading may be an important preoperative factor for decision-making in this scenario, as HGH ENBs were 2.1 times more likely to lead to eventual neck metastasis. Many physicians and institutions may also follow different preferences and guidelines for monitoring distant metastasis. Again, we believe that Hyams grading can play a valuable role in any systematic guideline. For instance, regular imaging may be considered for HGH ENBs as they may be 2.4 times more likely to metastasize distally. Aggressive treatments, such as induction chemotherapy and adjuvant radiotherapy, may also be more considered for patients with HGH ENBs. This has been alluded to by previous authors.[2,22]

To date, there are no universal guidelines for management of ENB, and many variables are considered in the multidisciplinary management of this rare malignancy. We thus recommend the LGH and HGH categorization of ENB as a constructive step in the comprehensive surveillance and management process. Multiple authors have suggested that Hyams grading could be utilized as an independent prognosticator.[16,17,34,38] Despite its apparent impact on survival, there is now mounting evidence that this information may be useful for elective treatment of the neck. Nakao *et al.*, Bell *et al.*, and Ow *et* al. exhibited that nodal metastasis and early recurrence was correlated with poorer survival.[2,39,40] Thus, our two main outcome variables, namely metastasis and survival, may be appropriately related.

The present study is not without limitations. There may be heterogeneity in correctly diagnosing ENB or accurately detecting and reporting metastasis. Some have suggested an increase in ENB diagnoses in recent decades likely due to improved differentiation of neuroendocrine malignancies.[41] Others recognize the possibility of confusing ENBs with other sinonasal tumors such as undifferentiated or neuroendocrine carcinomas.[2] There is also a possible lack of homogeneity in establishing Hyams grading per tumor. Some pathologists attest to the arbitrary nature of definitive grading for some ENB cases especially when a single tumor may have characteristics fitting multiple Hyams grades, such as the co-occurrence of necrosis and calcification.[14,24] Biopsy may also lead to sampling error as different parts of the tumor may contain different Hyams grades.[42,43] There might be a systematic difference in ENB treatment between institutions and time periods (i.e., decade of diagnosis), which may affect survival. It is worth noting that though all cases of dural metastasis were included as they were reported in the referenced studies, it is possible, if not otherwise specified, that some were not an indication of tumor progression but rather a result of local failure or lack of complete tumor resection. Additionally, it is very challenging to determine whether cervical metastases resulted from ENB primary recurrence, regional recurrence, or progression of disease. However, the data from the current study suggests that Hyams grading appears to demonstrate reliability as a marker of aggressive disease, which is

associated with any of the above scenarios. There is also the possibility of study and reporting bias, as positive and favorable data may be more likely to be submitted for publication. However, we think that the existing internal validity within each study in comparing LGH and LGH ENBs will, to some degree, control for such confounding factors. Even when considering these limitations, this meta-analysis benefits from a large cumulative population of many different institutions, patient demographics, and management guidelines.

Conclusion

The literature suggests that HGH ENBs, compared to LGH ENBs, were more likely to metastasize to the neck or distantly and to have lower overall survival rates. HGHs were more than twice as likely to metastasize whereas LGHs were three times as likely to have overall 5- or 10-year survival. Thus, Hyams grading can be an important and valuable tool in the surveillance and management of ENB.

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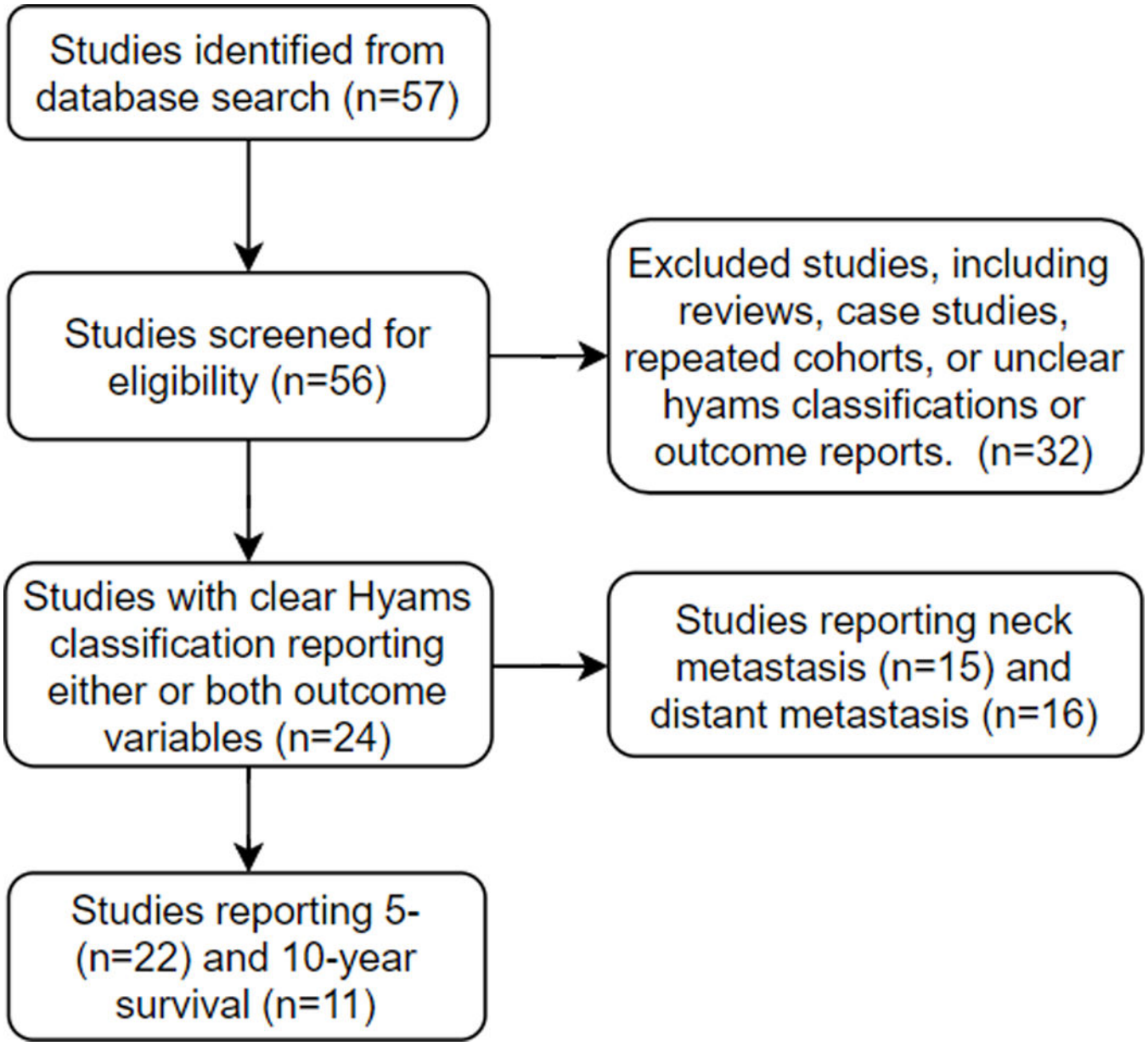

FIGURE 1.
Flowchart of study inclusion.

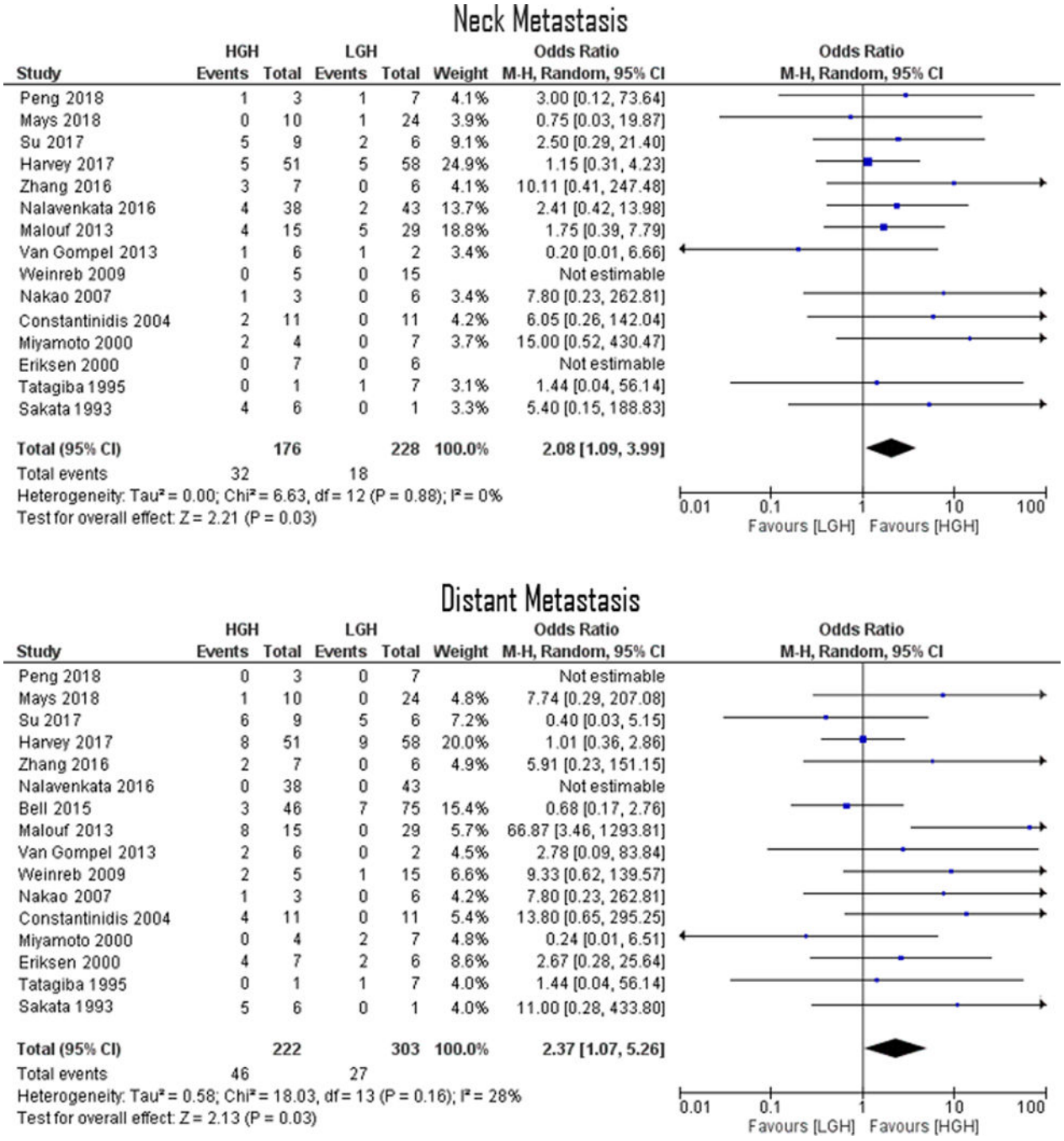

FIGURE 2.

Forrest Plots demonstrating an overall 2.08 (p=0.03) and 2.37 (p=0.03) ORs for ENB neck metastasis and distant metastasis, respectively. Lines are representative of the 95% confidence interval and boxes represent the post-operative intervention rate. Each box's size correlates to that study's size effect.

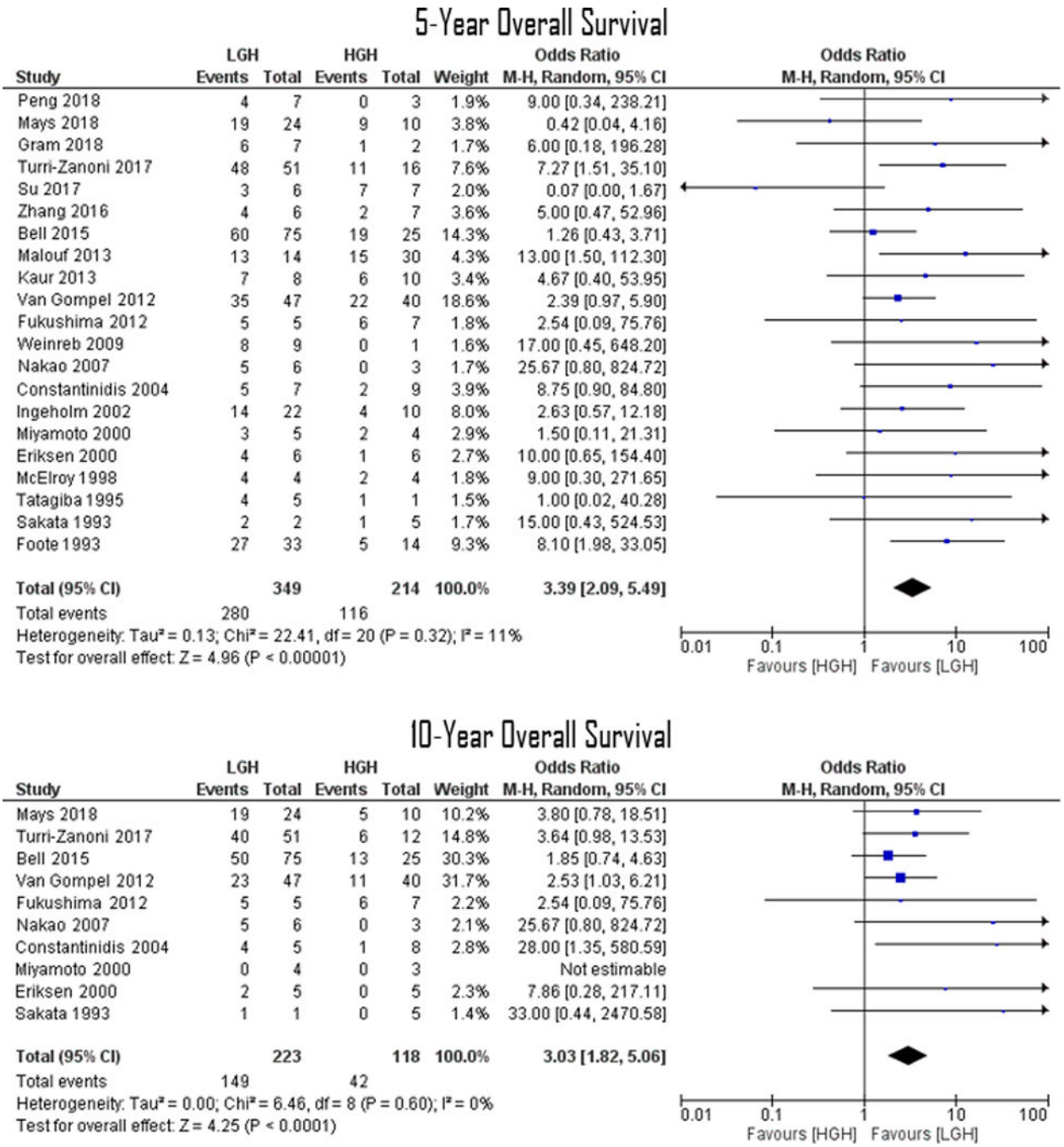

FIGURE 3.

Forrest Plots demonstrating an overall 3.39 (p<0.001) and 3.03 (p<0.001) ORs for ENB 5- and 10-year overall survival, respectively. Lines are representative of the 95% confidence interval and boxes represent the post-operative intervention rate. Each box's size correlates to that study's size effect.

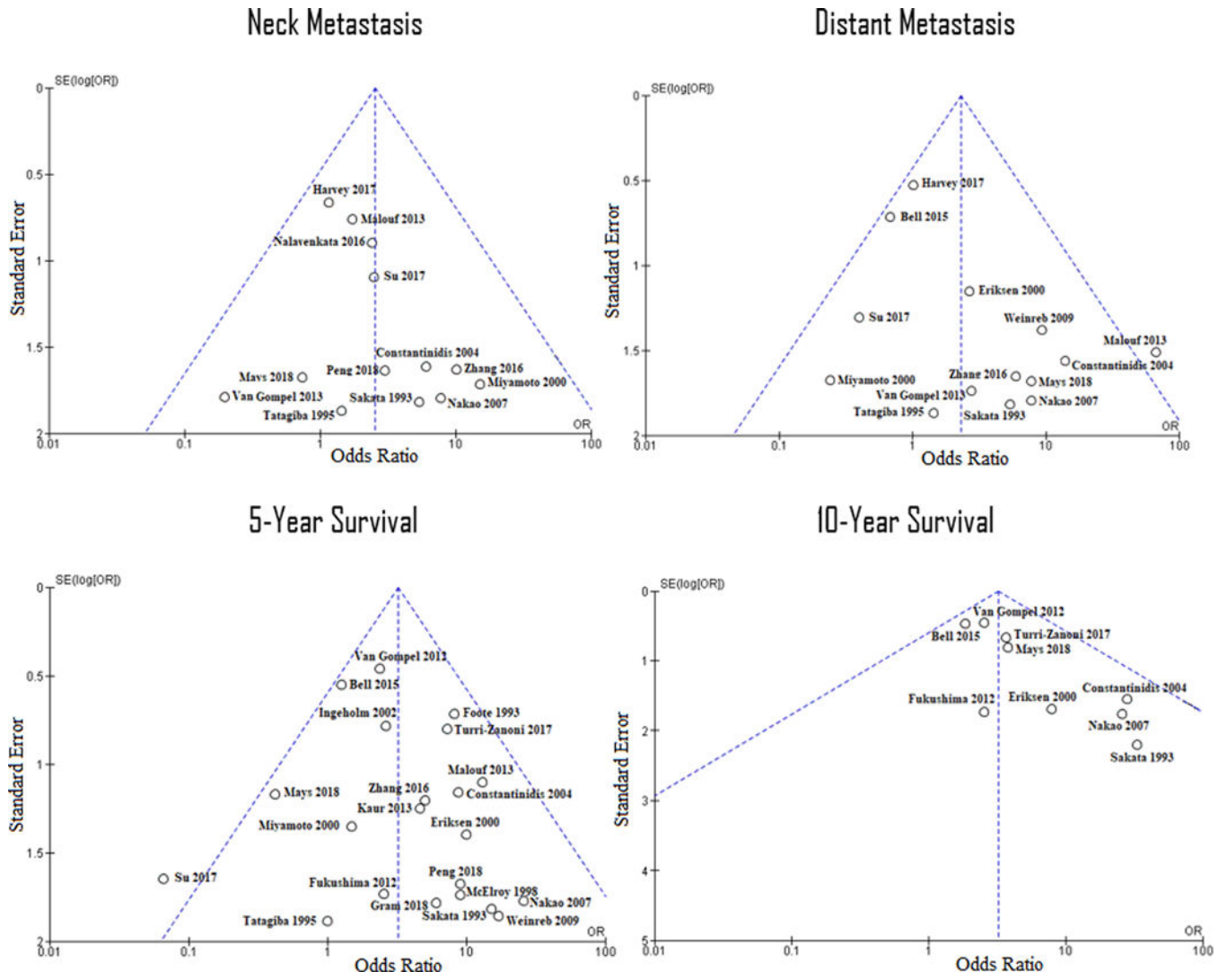

FIGURE 4.

Funnel plots of the four outcome variables for the evaluation of study bias. Dotted lines represent 95% confidence interval with a fixed population treatment effect, and the presence of a study outside these boundaries may suggest systematic bias. The only studies falling outside the boundaries were Malouf *et al.* and Su *et al.* distant metastasis and 5-year survival data, respectively.

Table 1:

Summary of patient demographics and outcome variables of studies used in the tumor metastasis meta-analysis.

Study	Study Years	Sample Size (% F)	Mean Age (range, yr)	Mean Follow-up (range, mo)	Hyams Grade	Neck Metastasis (%)	Distant Metastasis (%)
Peng, 2018[26]	2007–2015	10 (40)	46.5 (26–66)	N/A (6–76)	Low	1/7 (14.3)	0/7 (0)
					High	1/3 (33.3)	0/3 (0)
Mays, 2018[44]	1992–2012	35 (49)	43 (13–71)	N/A (8–240)	Low	1/24 (4.2)	0/24 (0)
					High	0/10 (0)	1/10 (10)
Harvey, 2017[10]	N/A	109 (46)	49.2	128.6 (6–421)	Low	5/58 (8.6)	9/58 (15.5)
					High	5/51 (9.8)	8/51 (15.7)
Su, 2017[45]	1993–2014	15 (47)	46.1 (11–78)	93.6 (1–266)	Low	2/6 (33.3)	5/6 (83.3)
					High	5/9 (55.6)	6/9 (66.7)
Zhang, 2016[42]	2000–2010	13 (38)	42.5 (15–69)	67.4 (23–116)	Low	0/6 (0)	0/6 (0)
					High	3/7 (42.9)	2/7 (28.6)
Nalavenkata, 2016[11]	1986–2013	113 (46)	49.7	41.5 *	Low	2/43 (4.7)	0/43 (0)
					High	4/38 (10.5)	0/38 (0)
Bell, 2015[2]	1990–2013	124 (39)	38.8 (7–90)	N/A (2–240)	Low	N/A	7/75 (9.3)
					High	N/A	3/25 (12)
Malouf, 2013[34]	1979–2009	44 (48)	42 (4–78)	147.7 (1–356)	Low	5/29 (17.2)	0/29 (0)
					High	4/15 (26.7)	8/15 (53.3)
Van Gompel, 2013[23]	1962–2012	8 (38)	52.6 (36–84)	27 (4–89)	Low	1/2 (50)	0/2 (0)
					High	1/6 (16.7)	2/6 (33.3)
Weinreb, 2009[46]	N/A	20 (35)	49.3 (20–79)	58.6 (3–152)	Low	0/15 (0)	1/15 (6.7)
					High	0/5 (0)	2/5 (40)
Nakao, 2007[39]	1979–2003	9 (44)	49.8 (25–73)	131.2 (6–325)	Low	0/6 (0)	0/6 (0)
					High	1/3 (33.3)	1/3 (33.3)
Constantinidis, 2004[21]	1975–2000	26 (50)	46.2 (10–84)	90.6 (4–259)	Low	0/11 (0)	0/11 (0)
					High	2/11 (18.2)	4/11 (36.4)
Miyamoto, 2000[47]	1970–1999	12 (42)	51 (17–85)	N/A (2–60)	Low	0/7 (0)	2/7 (28.6)
					High	2/4 (50)	0/4 (0)
Eriksen, 2000[48]	1977–1997	15 (40)	48.7 (14–83)	65 (8–139)	Low	0/6 (0)	2/6 (33.3)
					High	0/7 (0)	4/7 (57.1)
Tatagiba, 1995[49]	1978–1992	8 (63)	52.3 (29–70)	45 (6–84)	Low	1/7 (14.3)	1/7 (14.3)
					High	0/1 (0)	0/1 (0)
Sakata, 1993[50]	1978–1989	7 (29)	43.3 (17–73)	28.4 (2–120)	Low	0/1 (0)	0/1 (0)
					High	4/6 (66.7)	5/6 (83.3)

*=median instead of mean.

Table 2:

Summary of patient demographics and outcome variables of studies used in the 5- and 10-year overall survival meta-analyses.

Study	Study Years	Sample Size (% F)	Mean Age (range, yr)	Hyams Grade	5-Year Survival (%)	10-Year Survival (%)
Gram, 2018[51]	2000–2016	14 (29)	52.7 (17–81)	Low	6/7 (85.7)	N/A
				High	1/2 (50)	N/A
Peng, 2018[26]	2007–2015	10 (40)	46.5 (26–66)	Low	4/7 (57.1)	N/A
				High	0/3 (0)	N/A
Mays, 2018[44]	1992–2012	35 (49)	43 (13–71)	Low	19/24 (79.2)	19/24 (79.2)
				High	9/10 (90)	5/10 (50)
Turri-Zanoni, 2017[38]	2001–2015	98 (52)	51.2 (14–79)	Low	48/51 (94.1)	40/51 (78.4)
				High	11/16 (68.8)	6/12 (50)
Harvey, 2017[10]	N/A	109 (46)	49.2	Low	50/58 (86.2)	32/58 (55.2)
				High	44/51 (86.3)	27/51 (52.9)
Su, 2017[45]	1993–2014	15 (47)	46.1 (11–78)	Low	3/6 (50)	N/A
				High	7/7 (100)	N/A
Zhang, 2016[42]	2000–2010	13 (38)	42.5 (15–69)	Low	4/6 (66.7)	N/A
				High	2/7 (28.6)	N/A
Bell, 2015[2]	1990–2013	124 (39)	38.8 (7–90)	Low	60/75 (80)	50/75 (66.7)
				High	19/25 (76)	13/25 (52)
Van Gompel, 2012[22]	1962–2009	109 (44)	49 (12–90)	Low	35/47 (74.5)	23/47 (48.9)
				High	22/40 (55)	11/40 (27.5)
Malouf, 2013[34]	1979–2009	44 (48)	42 (4–78)	Low	13/14 (92.9)	N/A
				High	15/30 (50)	N/A
Kaur, 2013[52]	1995–2009	20 (14)	51 (31–70)	Low	7/8 (87.5)	N/A
				High	6/10 (60)	N/A
Fukushima, 2012[53]	1996–2009	12 (58)	34.9 (19–82)	Low	5/5 (100)	5/5 (100)
				High	6/7 (85.7)	6/7 (85.7)
Weinreb, 2009[46]	N/A	20 (35)	49.3 (20–79)	Low	8/9 (88.9)	N/A
				High	0/1 (0)	N/A
Nakao, 2007[39]	1979–2003	9 (44)	49.8 (25–73)	Low	5/6 (83.3)	5/6 (83.3)
				High	0/3 (0)	0/3 (0)
Constantinidis, 2004[21]	1975–2000	26 (50)	46.2 (10–84)	Low	5/7 (71.4)	4/5 (80)
				High	2/9 (22.2)	1/8 (12.5)
Ingeholm, 2002[54]	1978–2000	N/A	51.2 (13–82)	Low	14/22 (63.6)	N/A
				High	4/10 (40)	N/A
Miyamoto, 2000[47]	1970–1999	12 (42)	51 (17–85)	Low	3/5 (60)	0/4 (0)
				High	2/4 (50)	0/3 (0)
Eriksen, 2000[48]	1977–1997	15 (40)	48.7 (14–83)	Low	4/6 (66.7)	2/5 (40)

Study	Study Years	Sample Size (% F)	Mean Age (range, yr)	Hyams Grade	5-Year Survival (%)	10-Year Survival (%)
				High	1/6 (16.7)	0/5 (0)
McElroy, 1998[55]	1970–1995	10 (40)	48.2 (22–74)	Low	4/4 (100)	N/A
				High	2/4 (50)	N/A
Tatagiba, 1995[49]	1978–1992	8 (63)	52.3 (29–70)	Low	4/5 (80)	N/A
				High	1/1 (100)	N/A
Sakata, 1993[50]	1978–1989	7 (29)	43.3 (17–73)	Low	2/2 (100)	1/1 (100)
				High	1/5 (20)	0/5 (0)
Foote, 1993[56]	1951–1990	49 (45)	47.4 (3–79)	Low	27/33 (81.8)	N/A
				High	5/14 (35.7)	N/A