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Local Recurrence of Benign, Borderline, and Malignant Phyllodes Tumors of the Breast: A Systematic Review and Meta-analysis

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ABSTRACT

Background. This systematic review and meta-analysis aimed to investigate local recurrence (LR) rates among the three grades (benign, borderline, and malignant) of phyllodes tumors (PTs). The study also assessed various risk factors for LR.

Methods. Electronic articles published between 1 January 1995 and 31 May 2018, were searched and critically appraised. The authors independently reviewed the abstracts and extracted data for LR rates and LR risk factors.

Results. The review incorporated 54 studies with 9234 individual cases. The pooled LR rates were 8% for benign, 13% for borderline, and 18% for malignant PTs. The risk of LR was significantly increased by borderline versus benign PTs (odds ratio [OR] 2.00; 95% confidence interval [CI] 1.68–2.38) and malignant versus borderline PTs (OR 1.28; 95% CI 1.05–1.55). The significant risk factors for LR were mitoses, tumor border (infiltrating vs. pushing), stromal cellularity (moderate/severe vs. mild), stromal atypia (severe vs. mild/absent), stromal overgrowth (severe vs. mild/absent), and tumor necrosis (positive vs. negative). Age and tumor size were not associated with LR risk. The subgroup analysis showed that breast-conserving surgery versus mastectomy and positive versus negative surgical margins were significantly associated with an increased LR risk only in malignant PTs.

Conclusions. The risk of LR was significantly increased from benign to borderline to malignant PTs. Mitoses, tumor border, stromal cellularity, stromal atypia, stromal overgrowth, tumor necrosis, type of surgery, and surgical margin status may be risk factors for LR. Different management strategies could be considered for different PT grades.

Phyllodes tumors (PTs) are rare fibroepithelial lesions of the breast that account for 2–3% of all fibroepithelial breast tumors.[1,2] In general, PTs of the breast are classified into benign, borderline, and malignant grades based on a constellation of histologic characteristics, including degree of stromal cellularity, stromal atypia, mitoses, stromal overgrowth, and tumor border.[3]

The National Comprehensive Cancer Network (NCCN) guideline recommends wide excision with the intention of obtaining margins of 1 cm or more for each PT grade, implying that the pathologic grade of a tumor has little value for selecting a treatment method. This guideline has been supported by several retrospective studies.[4–10] Chaney et al.[11] reported that the crude local recurrence (LR) rates for both nonmalignant (4.3%, 3/70) and malignant

(3.3%, 1/30) PTs were comparable after a median follow-up period of 47 months. However, current evidence reflects the opposite findings.[12–18] A retrospective study with a median follow-up period of 80.4 months indicated that LR was considerably more frequent in malignant PTs (15.2%) than in benign (4.2%) and borderline (11.5%) PTs.[19] Similarly, a literature review confirmed that LR occurred more frequently in malignant groups (28%) than in non-malignant groups (15–17%).[20] Therefore, a more thorough analysis of LR among PTs is warranted.

We performed a systematic review and meta-analysis to provide the most up-to-date estimates of the LR rates for PTs with regard to pathologic grade. The study also assessed potential risk factors for LR.

METHODS

Search Strategy

A comprehensive literature search was performed using the PubMed, EMBASE, Medline, Web of Science, and Cochrane Library databases for studies published between 1 January 1995 and 31 May 2018. The following MeSH terms and their combinations were searched: (breast tumor/sarcoma/neoplasm) and (phyllodes or phyllode) and (recurrent/recurrence/prognosis/risk/relapse). Two authors (Y.L. and Y.C.) independently reviewed the titles and abstracts to screen and extract relevant articles.

Selection Criteria

The PICOS criteria for inclusion and exclusion were as follows:

P (participants): Studies of uni- or bilateral PTs with more than 50 patients were included.
I and C (intervention and control): Studies in which PT patients received surgical treatments were included.
O (outcome): Studies that included the LR rate with or without the following clinicopathologic factors were included: age, tumor size, surgery, surgical margin, tumor necrosis, stromal cellularity, stromal atypia, stromal overgrowth, mitoses, cellular pleomorphism, and tumor border. For risk factor analysis, only the studies reporting LR rates stratified by each risk factor were included. For age and tumor size, only the studies that used 40-year and 5-cm cutoff values, respectively, were included.
S (study type): Research articles published between 1 January 1995 and 31 May 2018, were included. All review papers, conference abstracts, meta-analyses, editorial/comment papers, and case reports were excluded from the study.

Quality Assessments

The quality of each eligible study was rated independently by two reviewers (Y.L. and K.C.) using the modified Newcastle–Ottawa scale.[21] A score of 0–9 (allocated as stars) was assigned to each study.

Data Extraction

A data collection sheet was developed to record the level of evidence, study quality, available outcomes, and risk factors. Two investigators (Y.L. and Y.C.) independently extracted data from these studies. To assess the presence of publication bias, we used funnel plots and Egger's test. The funnel plots were analyzed to determine the overall incidence of bias by plotting the event rate against the inverse of the standard error (SE).

Statistical Analysis

The analyses were performed using Stata 14.0 (StataCorp, College Station, TX, USA)[22] and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK).[23] We used a random-effects model to produce a pooled overall estimate for the LR rate with Stata 14.0. The odds ratio (OR) was used to compare dichotomous variables. All results were reported with 95% confidence intervals (CIs). Statistical heterogeneity between studies was assessed using the Chi square test and quantified using the I^2 statistic. A random-effects model was used when significant heterogeneity existed between studies. Otherwise, a fixed-effects model was used.[24]

RESULTS

Study Characteristics

All the included studies (Table 1; Fig. S1) were retrospective and had an evidence level of 3 or higher according to the criteria of the Center for Evidence-Based Medicine in Oxford, UK.[25] All observational studies had a quality score of 5 or higher (Newcastle–Ottawa scale) and were considered to have high quality.

LR Rate

The pooled data consisted of 54 studies with 9234 patients. The overall LR rate was 12% (95% CI 10–14%). The LR rates were 8% (95% CI 6–9%) for benign, 13% (95% CI 11–16%) for borderline, and 18% (95% CI 14–21%) for malignant PTs (Table 2; Fig. S2). The ranges of the 5-year cumulative LR risks were 3–23% for benign,

TABLE 1 Characteristics of the included studies

Study	Year	Time frame	Level of evidence[a]	Quality score[b]	Country	Age (years)[c]	Total patients (n)	Grade (n) Benign	Borderline	Malignant	Median follow-up (months)	Median time to LR[d] (months)	References
Reinfuss et al.	1996	1952–1988	3b	★★★★★★	Poland	NA[e]	170	92	19	59	96	NA	53
Yamada et al.	1997	1961–1993	3b	★★★★★	Japan	29.8	118	110	4	4	NA	NA	64
C. Zissis et al.	1998	1981–1995	3b	★★★★★★	Greece	34/46.5/52	84	55	14	11	79.8	NA	65
Chaney et al.	2000	1944–1998	4	★★★★★★★★	USA	41	101	59	12	30	47	NA	11
Niezabitowski et al.	2001	1952–1998	3b	★★★★★★★	Porland	49	118	52	24	42	60	NA	50
Asoglu et al.	2004	1971–2000	4	★★★★★★	USA	46	50	16	3	31	91	NA	39
Chen et al.	2005	1985–2003	3b	★★★★★★★★	Taiwan	37	172	131	12	29	71	NA	43
Sotheran et al.	2005	1982–2000	4	★★★★★★	UK	NA	50	29	12	9	35	25	29
Tan et al.[d,f]	2005	1992–2002	3b	★★★★★★★	Singapore	42	335	250	54	31	20.4	NA	66
Renner et al.	2005	1985–2000	3b	★★★★★	Austria	51	72	42	5	25	NA	NA	54
Ben Hassouna et al.	2006	1986–2001	3b	★★★★★★	Tunisia	39.6	106	62	16	28	43	NA	42
Hassan et al.	2006	1988–2003	4	★★★★★★	Egypt	42	79	31	27	21	60	NA	44
Cheng et al.	2006	1985–2004	4	★★★★★★★★	Taiwan	37	182	138	13	31	33	40.8 (1985–1996)/25 (1997–2004)	27
Barrio et al.	2007	1954–2005	4	★★★★★★★	USA	41.7	293	203	0	90	94.44	48	4
Belkacemi et al.	2007	1971–2003	4	★★★★★★★★	Switzerland	40	443	284	80	79	106	NA	40
Karim et al.	2009	1990–2006	3b	★★★★★★★★	Australia	43	65	34	23	8	63	20	33
Jung et al.	2010	1998–2006	3b	★★★★★	Korea	37.6	67	39	16	12	NA	14	13
Guillot et al.	2011	1994–2008	3b	★★★★★★	France	44	154	114	34	6	12.6	NA	10
Ga-Eon Kim et al.	2012	1999–2009	3b	★★★★★	Korea	41.17	82	50	22	10	29	NA	47
Jang et al.	2012	1995–2009	3b	★★★★★★	Korea	43	164	82	42	40	33.6	NA	46
Tan et al.[d]	2012	1992–2010	3b	★★★★★★★	Singapore	42	552	399	103	50	56.9	24.6	30
Tsang et al.	2012	NA	3b	★★★★★★★★	Hong Kong	44	152	90	42	20	75	43	58
Kim et al.	2013	2000–2010	3b	★★★★★★★	South Korea	40.5	193	145	33	15	65	43	15
Ho et al.	2013	2005–2009	4	★★★★★★	Hong Kong	45	185	120	48	17	42	NA	45
Ramakant et al.	2013	2003–2013	3b	★★★★★	India	39.24	150	77	24	49	NA	NA	52
Spitaleri et al.	2013	1999–2010	3b	★★★★★★★★	Italy	44	172	68	42	62	85	NA	20
Lightner Amy et al.[e]	2014	1986–2012	4	★★★★★	USA	45	64	32	11	21	NA	NA	38
Hui Wang et al.	2014	2002–2012	3b	★★★★★	China	40.7	246	125	55	47	NA	NA	61
Wei et al.	2014	1997–2012	3b	★★★★★★★	China	40	192	80	63	49	72.9	NA	62
Huang et al.	2014	1997–2004	3b	★★★★★	Taiwan	39	170	106	32	32	18.9	11.0–24.1	32
Wang et al.	2015	1995–2010	4	★★★★★	China	49	70	0	0	70	NA	NA	60

TABLE 1 Characteristics of the included studies

Study	Year	Time frame	Level of evidence[a]	Quality score[b]	Country	Age (years)[c]	Total patients (n)	Grade (n) Benign	Borderline	Malignant	Median follow-up (months)	Median time to LR[d] (months)	References
Yom et al.	2015	1989–2008	3b	★★★★★★★★	Korea	36.44	285	191	61	33	81.14	NA	19
Narayanakar et al.	2015	2001–2012	4	★★★★★★★	India	38	162	95	29	38	42	NA	16
Ng et al.	2015	NA	4	★★★★★★★	Singapore	43	97	57	29	11	30	NA	49
Akrami et al.	2015	1999–2013	3b	★★★★★	Iran	39	129	105	8	16	28	NA	37
Xiao et al.	2015	1993–2012	3b	★★★★★★★	China	NA	127	75	41	11	50.9	NA	63
Ouyang et al.	2016	2005–2013	3b	★★★★★★★★	China	37.3	225	225	0	0	35.5	NA	51
Borhani-Khomani et al.[e]	2016	1999–2014	4	★★★★★★★★★	Denmark	45.6	479	354	89	0	98	45 (mean)	26
Ruvalcaba-Limon et al.	2016	2005–2015	3b	★★★★★	Mexico	41.7	305	179	43	32	36.2	6	36
Moutte et al.	2016	2003–2013	3b	★★★★★★★	France	37.9	76	67	9	0	58	11.3	34
Bellezza et al.	2016	1988–2009	3b	★★★★★★	Italy	42	62	40	13	9	NA	NA	41
Kim et al.	2016	2000–2010	3b	★★★★★	Korea	40.1	194	153	27	16	NA	NA	14
Tremblay-LeMay et al.[e]	2017	1998–2010	3b	★★★★★★★	Canada	44.4	114	81	20	13	15.48/59.88/65.04[f]	NA	57
Moo et al.	2017	2003–2013	3b	★★★★★★	USA	35	216	216	0	0	35.5	NA	48
Matos et al.	2017	1976–2013	3b	★★★★★★★	Brazil	45.9	52	30	11	11	53.93	37.8 (mean)	9
Varghese et al.	2017	2005–2014	4	★★★★★★★	India	43	92	55	21	16	20	NA	59
Wang et al.	2018	2014–2015	3b	★★★★★	China	NA	54	33	11	10	NA	NA	17
Ganesh et al.	2018	1999–2017	3b	★★★★★★★	Canada	48.9	79	9	17	53	50[g]	13.3	12
Rodrigues et al.	2018	1999–2014	3b	★★★★★★★★	Canada	48	183	81	49	49	65	20.6	35
Choi et al.	2018	1981–2014	4	★★★★★★★	Korea	43	362	0	127	235	60	21.6	31
Co et al.	2018	1998–2014	4	★★★★★★★★	Hong Kong	44	469	281	124	64	85	NA	8
Zhou et al.	2018	2002–2013	3b	★★★★★★	China	41	404	168	184	52	46	NA	18
Chng et al.	2018	2006–2015	3b	★★★★★	Singapore	37.7	240	196	27	17	19.92	30.0	28
Slodkowska et al.	2018	1994–2012	3b	★★★★★★★	Canada	NA	94	45	28	21	56	NA	56
Sevinc	2018	1994–2017	3b	★★★★★★★	Turkey	40.6	122	108	14	0	51	NA	55

LR local recurrence, *NA* not available

[a] Level of evidence: according to the criteria of the Centre for Evidence-Based Medicine

[b] Stars represent the score of the study using the Newcastle–Ottawa Scale

[c] Age is represented by the median or the average age of the study population

[d] Tan et al. (2005) and Tan et al. (2012) had overlapping data. These two literatures were analyzed as one study. When we analyzed the LR rate, we used the Tan (2012) study because it contained a larger sample. When we analyzed the risk factors of LR, we used the Tan 2005 study because it reported more detailed data

[e] The study by Lightner Amy et al. included one invasive ductal carcinoma and two DCIS patients. The study by Borhani-Khomani et al. included two invasive ductal carcinoma, five DCIS, and three LCIS patients. The study by Tremblay-LeMay et al. included three invasive ductal carcinomas

[f] The median follow-up interval was 15.48 months for benign, 59.88 months for borderline, and 65.04 months for malignant PTs

[g] The median follow-up interval was for malignant grade

TABLE 2 Local recurrence (LR) rates of each grade of phyllodes tumors (PTs)

Grade of PTs	ES	95% CI	Study heterogeneity		No. of included patients	No. of studies	References
			I^2, %	p value			
Overall PTs	0.12	0.10–0.14	90.4	< 0.001	9234	54	4,5,8–20,26,28–39,41–65
Benign PTs	0.08	0.06–0.09	80.0	< 0.001	5693	51	4,5,8–20,26,28–38,41–59,61–65
Border PTs	0.13	0.11–0.16	62.2	< 0.001	1813	50	5,8–20,26,28–38,41–47,49–59,61–65
Malignant PTs	0.18	0.14–0.21	82.1	< 0.001	1728	49	4,5,8–20,28–33,35–39,41–47,49,50,52–54,56–65

ES effect size, *CI* confidence interval

9–55% for borderline, and 14.8–55% for malignant PTs (Table S1). The median time to recurrence was longer than 24 months in nine studies [4,9,15,26–30] and shorter than 24 months in eight studies.[12,13,31–36]

We extracted the ORs for the LR risk between each set of two PT grades from 54 studies.[4,8–20,26–65] We observed a significantly higher risk of LR for the borderline than for the benign grade (OR 2.00; 95% CI 1.68–2.38) and for the malignant than for the benign grade (OR 2.70; 95% CI 1.97–3.71). Likewise, malignant PTs had a significantly higher LR risk than borderline PTs (OR 1.28; 95% CI 1.05–1.55) (Fig. 1).

Age

Five studies[11,15,18,43,62] compared the LR risk between two age subgroups (≥ 40 vs. < 40 years: OR 0.95; 95% CI 0.47–1.93) (Fig. 2a). Four studies[27,31,32,62] analyzed the hazard ratios (HRs) of age for LR (≥ 40 vs. < 40 years: HR, 0.81; 95% CI 0.45–1.44) (Fig. S3a). No significant differences were found between the two subgroups. Six studies [10,46,54,58,63,66] compared the mean and median ages of patients with and without LR and found no significant differences except for Xiao et al.[63] (Table S2).

Tumor Size

Nine studies[11,15,16,18–20,39,43,62] evaluated tumor size (> 5 vs. ≤ 5 cm) as a risk factor for LR. The pooled result indicated that tumor size was not a significant risk factor for LR (OR 1.37; 95% CI 0.86–2.18) (Fig. 2b). Four studies[27,31,32,62] analyzed the HR of tumor size for LR, and observed no significant difference (HR, 1.44; 95% CI 0.87–2.38) (Fig. S3b). Six studies[10,43,46,54,58,66] compared the mean and median tumor sizes of patients with and without LR, but found no significant difference except for Jang et al.[46] (Table S3).

Treatment

Pooling of data from 22 studies[4,9,11,13,15,16,18–20,29,31,39,41–44,46,52,54,63,64,66] showed no significant difference in the LR risk between patients who underwent breast-conserving surgery (BCS) and those who had a mastectomy (OR 1.05; 95% CI 0.67–1.63) (Fig. 2c). The subgroup analysis included 6 studies for benign, 8, studies for borderline, and 10 studies for and malignant PTs. The results showed that BCS correlated with a significantly higher LR risk for malignant PTs (OR 2.32; 95% CI 1.01–5.30; p = 0.05; Fig. S4a).

Surgical Margin

A total of 24 studies[9,11,13,15,18–20,27,31–32,34,35,41,43,46,48,56–58,62,66] assessed the association between the surgical margin and LR. Most of the studies used a 1-cm width as an adequate surgical margin. Collectively, a positive versus a negative margin significantly increased the risk of LR (OR 3.32; 95% CI 2.18–5.06; HR, 5.00; 95% CI 3.09–8.10) (Fig. 2d; Fig. S3c). Six, five, and five studies[15,20,29,34,35,48] reported LR rates for the benign, borderline, and malignant grades, respectively (Fig. S4b). A positive surgical margin was significantly associated with a higher LR risk for malignant PTs (OR 6.85; 95% CI 1.58–29.64), but only a tendency for an increase in the LR risk was observed for benign (OR 3.95; 95% CI 0.58–26.76) and borderline (OR 1.60; 95% CI 0.42–6.07) PTs (Fig. S4b).

Pathologic Parameters

Associations between frequently used pathologic parameters and the risk of LR also were scrutinized (Table 3; Fig. S5). The pooled results showed that an increased risk of LR mitoses was significantly associated with 10/10 HPF or higher (OR 2.89; 95% CI 1.40–5.97), an infiltrating versus a pushing border (OR 2.79; 95% CI 1.43–5.46), moderate/severe versus mild stromal cellularity (OR 2.63; 95% CI 1.58–4.39), severe versus mild/absent stromal atypia (OR 2.32, 95% CI 1.08–4.96), severe versus mild/absent stromal overgrowth (OR 2.04, 95% CI 1.03–4.04), and positive versus negative tumor necrosis (OR 2.00; 95% CI 1.17–3.40).

a

Study or Subgroup	Borderline PT Events	Total	Benign PT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Reinfuss, 1996	3	19	4	92	0.7%	4.13 [0.84, 20.21]	1996
Yamada, 1997	0	4	6	110	0.3%	1.79 [0.09, 36.87]	1997
C. Zissis, 1998	2	14	0	55	0.1%	22.20 [1.00, 491.69]	1998
Chaney, 2000	0	12	3	59	0.7%	0.65 [0.03, 13.31]	2000
Niezabitowski, 2001	1	24	2	52	0.7%	1.09 [0.09, 12.61]	2001
Asoglu, 2004	2	3	0	0		Not estimable	2004
Renner, 2005	2	5	4	42	0.3%	6.33 [0.80, 49.92]	2005
Chen, 2005	0	12	19	131	2.0%	0.23 [0.01, 4.06]	2005
Sotheran, 2005	3	12	1	29	0.3%	9.33 [0.86, 101.30]	2005
Hassan, 2006	7	27	3	31	1.2%	3.27 [0.75, 14.20]	2006
Ben Hassouna, 2006	5	16	3	62	0.5%	8.94 [1.86, 42.94]	2006
Cheng, 2006	0	13	20	138	2.2%	0.21 [0.01, 3.74]	2006
Barrio, 2007	0	0	23	203		Not estimable	2007
Belkacemi, 2008	23	80	31	384	5.8%	3.29 [1.79, 6.07]	2008
Karim, 2009	4	23	3	34	1.2%	2.18 [0.44, 10.80]	2009
Jung, 2010	2	16	4	39	1.2%	1.25 [0.21, 7.62]	2010
Guillot, 2011	8	34	7	114	1.5%	4.70 [1.56, 14.15]	2011
Jang, 2012	9	42	12	82	3.8%	1.59 [0.61, 4.15]	2012
Tsang, 2012	12	42	15	90	4.1%	2.00 [0.84, 4.77]	2012
Ga-Eon Kim, 2012	3	22	5	50	1.6%	1.42 [0.31, 6.55]	2012
Tan, 2012	16	103	48	399	9.9%	1.34 [0.73, 2.48]	2012
Kim, 2013	6	33	5	145	0.9%	6.22 [1.77, 21.85]	2013
Ramakant, 2013	16	24	16	77	2.6%	2.72 [1.02, 7.26]	2013
Ho, 2013	2	48	7	120	2.3%	0.70 [0.14, 3.51]	2013
Spitaleri, 2013	6	42	3	68	1.2%	3.61 [0.85, 15.31]	2013
Wang, Hui., 2014	13	55	17	125	4.7%	1.97 [0.88, 4.40]	2014
Wei, 2014	10	63	9	80	4.0%	1.49 [0.57, 3.92]	2014
Huang, 2014	3	32	16	16	4.0%	0.58 [0.16, 2.14]	2014
Lightner Amy, 2014	0	11	1	32	0.5%	0.91 [0.03, 24.05]	2014
Wang, F., 2015	0	0	0	0		Not estimable	2015
Ouyang, 2015	0	0	20	225		Not estimable	2015
Narayanakar, 2015	12	29	15	95	2.4%	3.76 [1.50, 9.47]	2015
Yom, 2015	7	61	8	191	2.0%	2.97 [1.03, 8.55]	2015
Xiao, 2015	7	41	11	75	2.8%	1.20 [0.43, 3.37]	2015
Akrami, 2015	1	8	4	105	0.3%	3.61 [0.35, 36.75]	2015
Ng, 2015	5	29	3	57	1.0%	3.75 [.83, 16.97]	2015
Ruvalcaba-Limon, 2016	3	43	12	179	2.6%	1.04 [0.28, 3.87]	2016
Bellezza, 2016	3	13	7	40	1.6%	1.41 [0.31, 6.51]	2016
Moutte, 2016	1	9	2	67	0.3%	4.06 [0.33, 50.00]	2016
Borhani-Khomani, 2016	8	89	22	354	4.8%	1.49 [0.64, 3.47]	2016
Kim, 2016	6	27	5	153	0.7%	8.46 [2.37, 30.17]	2016
Varghese, 2017	1	21	5	55	1.6%	0.50 [0.05, 4.55]	2017
Matos, 2017	5	11	9	30	1.6%	1.94 [0.47, 8.05]	2017
Tremblay-LeMay, 2017	2	20	3	81	0.6%	2.89 [0.45, 18.58]	2017
Moo, 2017	0	0	4	216		Not estimable	2017
Zhou, 2018	26	184	6	168	3.2%	4.44 [1.78, 11.09]	2018
Choi, 2018	23	127	0	0		Not estimable	2018
Ganesh, 2018	0	17	0	9		Not estimable	2018
Slodknowska, 2018	3	28	10	45	4.1%	0.42 [0.10, 1.68]	2018
Chng, 2018	2	27	9	196	1.2%	1.66 [0.34, 8.13]	2018
Co, 2018	14	124	21	281	6.8 %	1.58 [0.77, 3.21]	2018
Sevinc 2018	0	14	0	108		Not estimable	2018
Rodrigues, 2018	4	49	5	81	2.1%	1.35 [0.34, 5.29]	2018
Wang, K., 2018	3	11	6	33	1.3%	1.69 [0.34, 8.31]	2018
Total (95% CI)		**1813**		**5693**	**100.0%**	**2.00 [1.68, 2.38]**	
Total events	288		474				

Heterogeneity: Chi² = 53.47, df = 45 (P = 0.18); I² = 16%
Test for overall effect: Z = 7.87 (P < 0.00001)

FIG. 1 **a** Forest plot showing the pooled odds ratios (ORs) of local recurrence (LR) for borderline versus benign) phyllodes tumors (PTs). **b** Forest plot showing the pooled ORs of LR for malignant versus benign PTs. **c** Forest plot showing the pooled ORs of LR for malignant versus borderline PTs

Sensitivity Analysis and Publication Bias

The sensitivity analysis included 40 retrospective studies[4,8–12,15,16,18–20,26,27,29–31,33–35,39,40,42–46,48–51,53,55–59,62,63,65,66] with a score of six or more stars on the modified Newcastle–Ottawa scale. No significant changes in the outcomes were noted. No significant publication bias was observed in the funnel plots (Fig. S6).

DISCUSSION

To date, no large-scale prospective studies of PTs have been conducted due to their low incidence. Therefore, the existing guidelines for PTs are based on retrospective studies, and data are limited. We performed a systematic review and meta-analysis to evaluate LR rates comprehensively for each PT grade and to investigate the related risk factors.
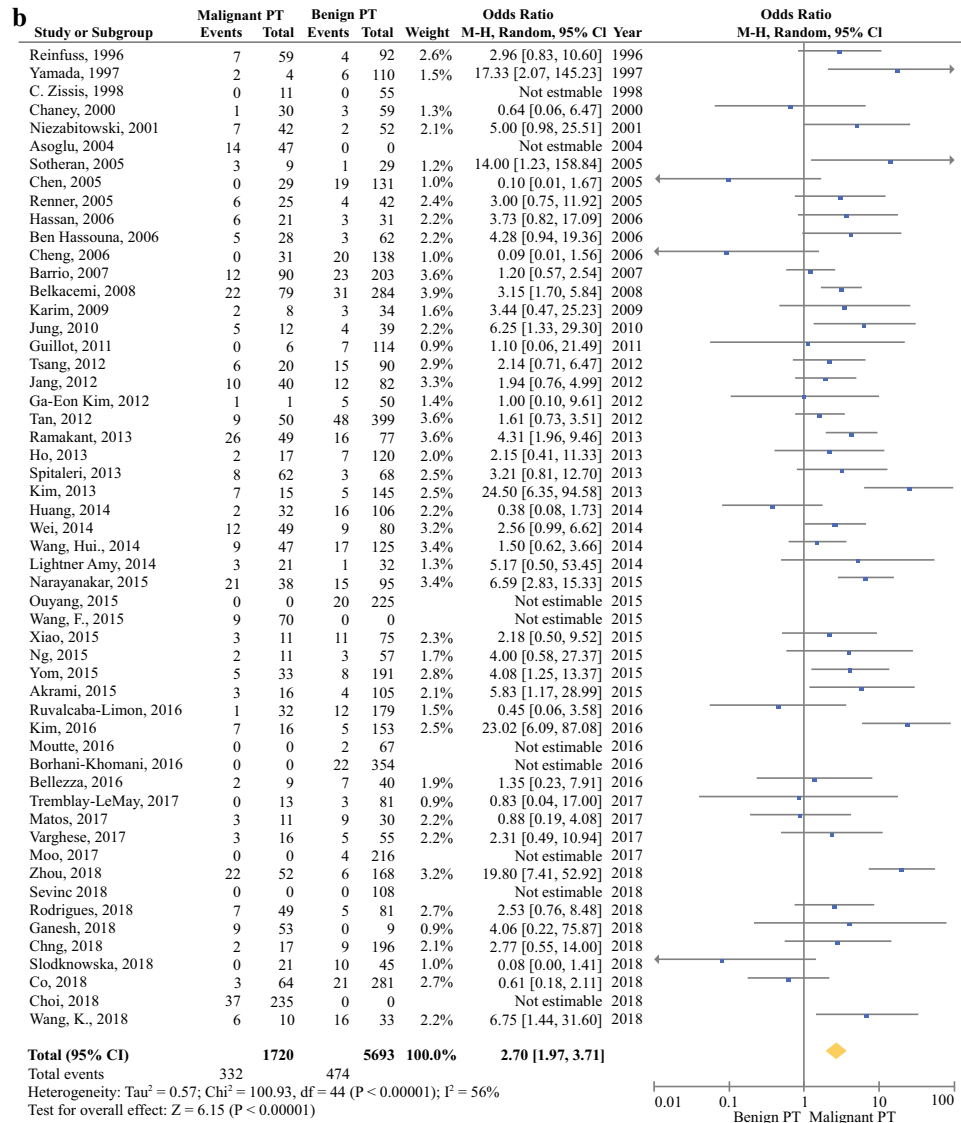
b

Study or Subgroup	Malignant PT Events	Malignant PT Total	Benign PT Events	Benign PT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Reinfuss, 1996	7	59	4	92	2.6%	2.96 [0.83, 10.60]	1996
Yamada, 1997	2	4	6	110	1.5%	17.33 [2.07, 145.23]	1997
C. Zissis, 1998	0	11	0	55		Not estmable	1998
Chaney, 2000	1	30	3	59	1.3%	0.64 [0.06, 6.47]	2000
Niezabitowski, 2001	7	42	2	52	2.1%	5.00 [0.98, 25.51]	2001
Asoglu, 2004	14	47	0	0		Not estmable	2004
Sotheran, 2005	3	9	1	29	1.2%	14.00 [1.23, 158.84]	2005
Chen, 2005	0	29	19	131	1.0%	0.10 [0.01, 1.67]	2005
Renner, 2005	6	25	4	42	2.4%	3.00 [0.75, 11.92]	2005
Hassan, 2006	6	21	3	31	2.2%	3.73 [0.82, 17.09]	2006
Ben Hassouna, 2006	5	28	3	62	2.2%	4.28 [0.94, 19.36]	2006
Cheng, 2006	0	31	20	138	1.0%	0.09 [0.01, 1.56]	2006
Barrio, 2007	12	90	23	203	3.6%	1.20 [0.57, 2.54]	2007
Belkacemi, 2008	22	79	31	284	3.9%	3.15 [1.70, 5.84]	2008
Karim, 2009	2	8	3	34	1.6%	3.44 [0.47, 25.23]	2009
Jung, 2010	5	12	4	39	2.2%	6.25 [1.33, 29.30]	2010
Guillot, 2011	0	6	7	114	0.9%	1.10 [0.06, 21.49]	2011
Tsang, 2012	6	20	15	90	2.9%	2.14 [0.71, 6.47]	2012
Jang, 2012	10	40	12	82	3.3%	1.94 [0.76, 4.99]	2012
Ga-Eon Kim, 2012	1	1	5	50	1.4%	1.00 [0.10, 9.61]	2012
Tan, 2012	9	50	48	399	3.6%	1.61 [0.73, 3.51]	2012
Ramakant, 2013	26	49	16	77	3.6%	4.31 [1.96, 9.46]	2013
Ho, 2013	2	17	7	120	2.0%	2.15 [0.41, 11.33]	2013
Spitaleri, 2013	8	62	3	68	2.5%	3.21 [0.81, 12.70]	2013
Kim, 2013	7	15	5	145	2.5%	24.50 [6.35, 94.58]	2013
Huang, 2014	2	32	16	106	2.2%	0.38 [0.08, 1.73]	2014
Wei, 2014	12	49	9	80	3.2%	2.56 [0.99, 6.62]	2014
Wang, Hui., 2014	9	47	17	125	3.4%	1.50 [0.62, 3.66]	2014
Lightner Amy, 2014	3	21	1	32	1.3%	5.17 [0.50, 53.45]	2014
Narayanakar, 2015	21	38	15	95	3.4%	6.59 [2.83, 15.33]	2015
Ouyang, 2015	0	0	20	225		Not estimable	2015
Wang, F., 2015	9	70	0	0		Not estimable	2015
Xiao, 2015	3	11	11	75	2.3%	2.18 [0.50, 9.52]	2015
Ng, 2015	2	11	3	57	1.7%	4.00 [0.58, 27.37]	2015
Yom, 2015	5	33	8	191	2.8%	4.08 [1.25, 13.37]	2015
Akrami, 2015	3	16	4	105	2.1%	5.83 [1.17, 28.99]	2015
Ruvalcaba-Limon, 2016	1	32	12	179	1.5%	0.45 [0.06, 3.58]	2016
Kim, 2016	7	16	5	153	2.5%	23.02 [6.09, 87.08]	2016
Moutte, 2016	0	0	2	67		Not estimable	2016
Borhani-Khomani, 2016	0	0	22	354		Not estimable	2016
Bellezza, 2016	2	9	7	40	1.9%	1.35 [0.23, 7.91]	2016
Tremblay-LeMay, 2017	0	13	3	81	0.9%	0.83 [0.04, 17.00]	2017
Matos, 2017	3	11	9	30	2.2%	0.88 [0.19, 4.08]	2017
Varghese, 2017	3	16	5	55	2.2%	2.31 [0.49, 10.94]	2017
Moo, 2017	0	0	4	216		Not estimable	2017
Zhou, 2018	22	52	6	168	3.2%	19.80 [7.41, 52.92]	2018
Sevinc 2018	0	0	5	108		Not estimable	2018
Rodrigues, 2018	7	49	5	81	2.7%	2.53 [0.76, 8.48]	2018
Ganesh, 2018	9	53	0	9	0.9%	4.06 [0.22, 75.87]	2018
Chng, 2018	2	17	9	196	2.1%	2.77 [0.55, 14.00]	2018
Slodknowska, 2018	0	21	10	45	1.0%	0.08 [0.00, 1.41]	2018
Co, 2018	3	64	21	281	2.7%	0.61 [0.18, 2.11]	2018
Choi, 2018	37	235	0	0		Not estimable	2018
Wang, K., 2018	6	10	16	33	2.2%	6.75 [1.44, 31.60]	2018
Total (95% CI)		**1720**		**5693**	**100.0%**	**2.70 [1.97, 3.71]**	
Total events	332		474				

Heterogeneity: Tau^2 = 0.57; Chi^2 = 100.93, df = 44 (P < 0.00001); I^2 = 56%
Test for overall effect: Z = 6.15 (P < 0.00001)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
Benign PT Malignant PT

FIG. 1 continued

LR Rate

The World Health Organization (WHO) reported that LR of PTs occurred at an overall rate of 21% with a range of 10–17% for benign, 14–25% for borderline, and 23–30% for malignant PTs.[67] For an Asian population ($n = 605$), Tan et al.[30] reported that the LR rates were 10.9% for benign, 14.4% for borderline, and 29.6% for malignant PTs, suggesting that the LR risks for borderline and benign PTs were closer. In contrast, Belkacemi et al.[40] analyzed multicenter data from Europe ($n = 443$) and reported that borderline (29%) and malignant (28%) PTs had similar LR risks, which were higher than those for benign PTs (11%).

In this study, the LR rates increased from benign (8%; range, 6–9%) to borderline (13%; range, 11–16%) to malignant (18%; range, 14–21%) PTs. The lower limit of

the pooled OR of the malignant versus the borderline PTs was close to 1.00 (OR 1.28; 95% CI 1.05–1.55). Additionally, the 95% CIs of the pooled LR rates for the borderline and malignant PTs overlapped, indicating that some borderline cases may recur at a risk as high as for malignant PTs. Studies showed genomic similarity between these two PT grades.

Lae et al.[68] reported that the chromosomal imbalances in borderline and malignant PTs were analogous and that only two PT grades (benign and malignant) could be distinguished on a genomic basis. Moreover, a Singapore group performed exome sequencing of PTs and reported that compared with benign PTs, borderline and malignant PTs exhibited additional mutations coupled with putative copy number alterations in NF1, RB1, TP53, PIK3CA, ERBB4, and EGFR, which are known cancer driver genes.[69] These
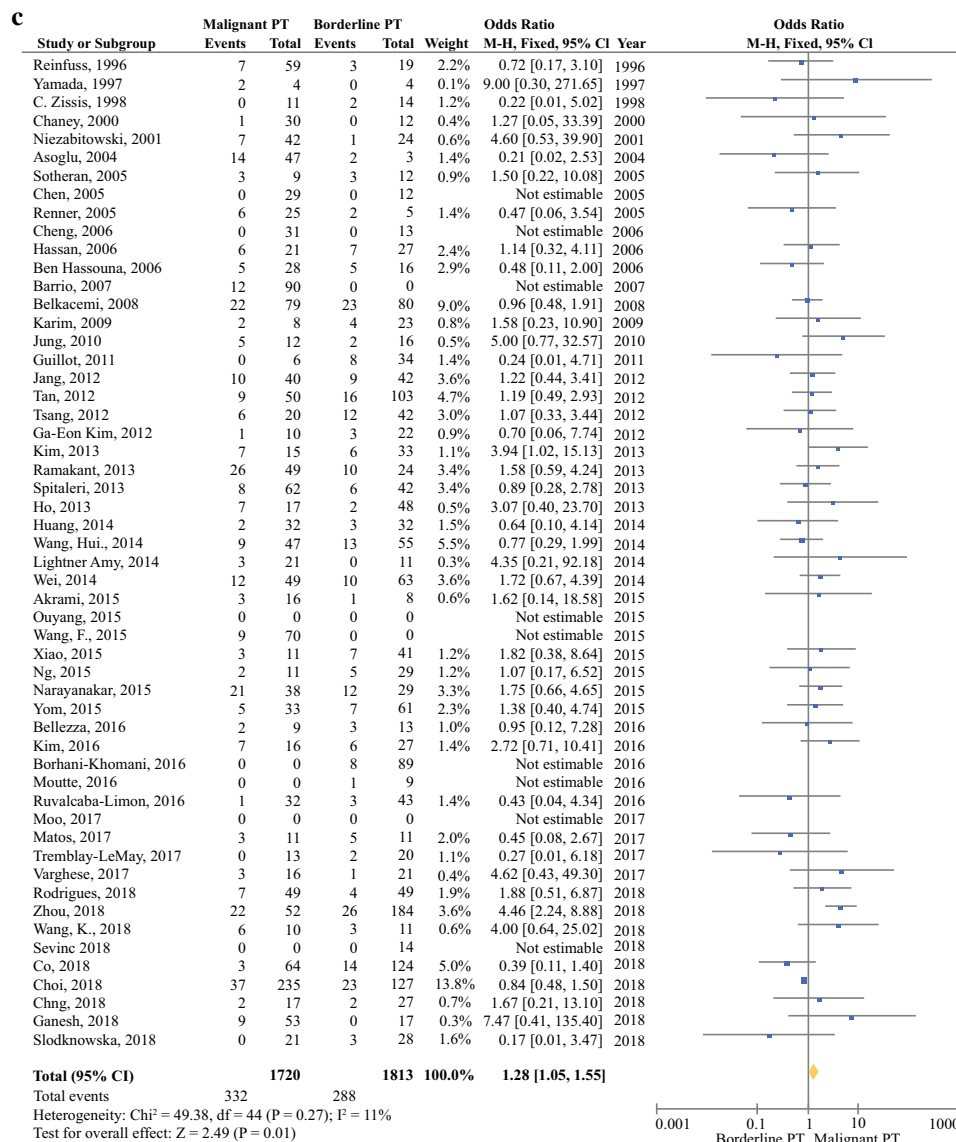
c

Study or Subgroup	Malignant PT Events	Total	Borderline PT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year	Odds Ratio M-H, Fixed, 95% CI
Reinfuss, 1996	7	59	3	19	2.2%	0.72 [0.17, 3.10]	1996	
Yamada, 1997	2	4	0	4	0.1%	9.00 [0.30, 271.65]	1997	
C. Zissis, 1998	0	11	2	14	1.2%	0.22 [0.01, 5.02]	1998	
Chaney, 2000	1	30	0	12	0.4%	1.27 [0.05, 33.39]	2000	
Niezabitowski, 2001	7	42	1	24	0.6%	4.60 [0.53, 39.90]	2001	
Asoglu, 2004	14	47	2	3	1.4%	0.21 [0.02, 2.53]	2004	
Sotheran, 2005	3	9	3	12	0.9%	1.50 [0.22, 10.08]	2005	
Chen, 2005	0	29	0	12		Not estimable	2005	
Renner, 2005	6	25	2	5	1.4%	0.47 [0.06, 3.54]	2005	
Cheng, 2006	0	31	0	13		Not estimable	2006	
Hassan, 2006	6	21	7	27	2.4%	1.14 [0.32, 4.11]	2006	
Ben Hassouna, 2006	5	28	5	16	2.9%	0.48 [0.11, 2.00]	2006	
Barrio, 2007	12	90	0	0		Not estimable	2007	
Belkacemi, 2008	22	79	23	80	9.0%	0.96 [0.48, 1.91]	2008	
Karim, 2009	2	8	4	23	0.8%	1.58 [0.23, 10.90]	2009	
Jung, 2010	5	12	2	16	0.5%	5.00 [0.77, 32.57]	2010	
Guillot, 2011	0	6	8	34	1.4%	0.24 [0.01, 4.71]	2011	
Jang, 2012	10	40	9	42	3.6%	1.22 [0.44, 3.41]	2012	
Tan, 2012	9	50	16	103	4.7%	1.19 [0.49, 2.93]	2012	
Tsang, 2012	6	20	12	42	3.0%	1.07 [0.33, 3.44]	2012	
Ga-Eon Kim, 2012	1	10	3	22	0.9%	0.70 [0.06, 7.74]	2012	
Kim, 2013	7	15	6	33	1.1%	3.94 [1.02, 15.13]	2013	
Ramakant, 2013	26	49	10	24	3.4%	1.58 [0.59, 4.24]	2013	
Spitaleri, 2013	8	62	6	42	3.4%	0.89 [0.28, 2.78]	2013	
Ho, 2013	7	17	2	48	0.5%	3.07 [0.40, 23.70]	2013	
Huang, 2014	2	32	3	32	1.5%	0.64 [0.10, 4.14]	2014	
Wang, Hui., 2014	9	47	13	55	5.5%	0.77 [0.29, 1.99]	2014	
Lightner Amy, 2014	3	21	0	11	0.3%	4.35 [0.21, 92.18]	2014	
Wei, 2014	12	49	10	63	3.6%	1.72 [0.67, 4.39]	2014	
Akrami, 2015	3	16	1	8	0.6%	1.62 [0.14, 18.58]	2015	
Ouyang, 2015	0	0	0	0		Not estimable	2015	
Wang, F., 2015	9	70	0	0		Not estimable	2015	
Xiao, 2015	3	11	7	41	1.2%	1.82 [0.38, 8.64]	2015	
Ng, 2015	2	11	5	29	1.2%	1.07 [0.17, 6.52]	2015	
Narayanakar, 2015	21	38	12	29	3.3%	1.75 [0.66, 4.65]	2015	
Yom, 2015	5	33	7	61	2.3%	1.38 [0.40, 4.74]	2015	
Bellezza, 2016	2	9	3	13	1.0%	0.95 [0.12, 7.28]	2016	
Kim, 2016	7	16	6	27	1.4%	2.72 [0.71, 10.41]	2016	
Borhani-Khomani, 2016	0	0	8	89		Not estimable	2016	
Moutte, 2016	0	0	1	9		Not estimable	2016	
Ruvalcaba-Limon, 2016	1	32	3	43	1.4%	0.43 [0.04, 4.34]	2016	
Moo, 2017	0	0	0	0		Not estimable	2017	
Matos, 2017	3	11	5	11	2.0%	0.45 [0.08, 2.67]	2017	
Tremblay-LeMay, 2017	0	13	2	20	1.1%	0.27 [0.01, 6.18]	2017	
Varghese, 2017	3	16	1	21	0.4%	4.62 [0.43, 49.30]	2017	
Rodrigues, 2018	7	49	4	49	1.9%	1.88 [0.51, 6.87]	2018	
Zhou, 2018	22	52	26	184	3.6%	4.46 [2.24, 8.88]	2018	
Wang, K., 2018	6	10	3	11	0.6%	4.00 [0.64, 25.02]	2018	
Sevinc 2018	0	0	0	14		Not estimable	2018	
Co, 2018	3	64	14	124	5.0%	0.39 [0.11, 1.40]	2018	
Choi, 2018	37	235	23	127	13.8%	0.84 [0.48, 1.50]	2018	
Chng, 2018	2	17	2	27	0.7%	1.67 [0.21, 13.10]	2018	
Ganesh, 2018	9	53	0	17	0.3%	7.47 [0.41, 135.40]	2018	
Slodknowska, 2018	0	21	3	28	1.6%	0.17 [0.01, 3.47]	2018	
Total (95% CI)		**1720**		**1813**	**100.0%**	**1.28 [1.05, 1.55]**		
Total events	332		288					

Heterogeneity: Chi² = 49.38, df = 44 (P = 0.27); I² = 11%
Test for overall effect: Z = 2.49 (P = 0.01)

Odds Ratio M-H, Fixed, 95% CI — scale 0.001 0.1 1 10 1000
Borderline PT   Malignant PT

FIG. 1 continued

findings suggest that borderline PTs may deserve the same attention as malignant PTs during surgical decision making.

Notably, some benign PTs recurred as borderline and malignant PTs.[15,19,30,32,34,45,52,57,63] Our pooled data showed that 26% (range, 13–38%) of recurrent benign and 21% (range, 8–33%) of recurrent borderline PTs underwent upgrade (Fig. S7). Cautious pathologic diagnosis and follow-up evaluation are necessary for benign and borderline PTs.

Risk Factors for Local Recurrence

A recent study [70] reported that tumor size was significantly associated with metastasis in malignant PTs.

However, whether tumor size is a predictor of LR is unclear. Several studies showed that tumor size was not associated with LR,[7,27,71] which was confirmed in our pooled analysis. In our study, we used 50 mm as the cutoff value because this value was used in most of the included studies, and whether the use of a different cutoff value would influence the results was unclear.

The surgical margin status (positive vs. negative) is widely accepted as an important risk factor for LR. The NCCN guideline recommends wide local excision with the intention of obtaining margins of 1 cm or more for each PT grade. However, their supporting evidence came from a retrospective study[72] that was limited by a small sample size at a single institution.

In the current study, we observed that a positive margin and BCS both significantly correlated with a higher LR risk

a Age

Study or Subgroup	Age ≥ 40yrs Events	Total	Age < 40yrs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Chaney, 2000	2	51	2	50	9.0%	0.98 [0.13, 7.24]	2000
Chen, 2005	13	73	6	99	19.6%	3.36 [1.21, 9.32]	2005
Kim, 2013	10	104	8	89	20.3%	1.08 [0.41, 2.86]	2013
Wei, 2014	15	129	16	63	23.7%	0.39 [0.18, 0.84]	2014
Zhou, 2018	28	233	26	171	27.3%	0.76 [0.43, 1.35]	2018
Total (95% CI)		**590**		**472**	**100.0%**	**0.95 [0.47, 1.93]**	
Total events	68		58				

Heterogeneity: Tau² = 0.39; Chi² = 11.27, df = 4 (P = 0.027); I² = 65%
Test for overall effect: Z = 0.13 (P = 0.89)
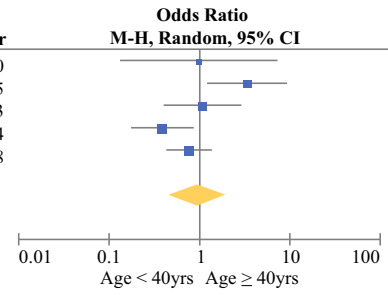
b Tumor size

Study or Subgroup	T > 5cm Events	Total	T ≤ 5cm Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Chaney, 2000	3	45	1	41	3.6%	2.86 [0.29, 28.62]	2000
Asoglu, 2004	9	20	4	27	8.3%	4.70 [1.18, 18.69]	2004
Chen, 2005	6	57	13	115	12.4%	0.92 [0.33, 2.57]	2005
Kim, 2013	5	64	13	129	11.6%	0.76 [0.26, 2.22]	2013
Spitaleri, 2013	7	62	13	105	13.1%	0.90 [0.34, 2.39]	2013
Wei, 2014	16	59	12	100	15.6%	2.73 [1.19, 6.27]	2014
Yom, 2015	1	52	19	231	4.5%	0.22 [0.03, 1.67]	2015
Narayanakar, 2015	43	134	5	28	12.3%	2.17 [0.77, 6.11]	2015
Zhou, 2018	14	124	27	265	18.7%	1.12 [0.57, 2.22]	2018
Total (95% CI)		**617**		**1041**	**100.0%**	**1.37 [0.86, 2.18]**	
Total events	104		107				

Heterogeneity: Tau² = 0.18; Chi² = 12.81, df = 8 (P = 0.12); I² = 38%
Test for overall effect: Z = 1.34 (P = 0.18)
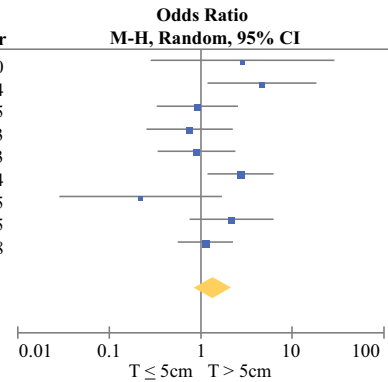
c Surgery

Study or Subgroup	Breast-conserving surgery Events	Total	Mastectomy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Yamada, 1997	8	106	0	2	1.7%	0.43 [0.02, 9.73]	1997
Chaney, 2000	2	47	2	54	3.2%	1.16 [0.16, 8.54]	2000
Asoglu, 2004	8	22	8	28	5.6%	1.43 [0.43, 4.72]	2004
Chen, 2005	19	126	0	46	2.0%	16.87 [1.00, 285.33]	2005
Sotheran, 2005	7	42	0	8	1.8%	3.59 [0.19, 69.24]	2005
Renner, 2005	11	55	4	15	5.1%	0.69 [0.18, 2.58]	2005
Tan, 2005	38	311	4	23	5.9%	0.66 [0.21, 2.05]	2005
Hassan, 2006	14	46	2	33	4.4%	6.78 [1.42, 32.33]	2006
Ben Hassouna, 2006	3	82	10	24	4.8%	0.05 [0.01, 0.22]	2006
Barrio, 2007	31	242	4	48	6.0%	1.62 [0.54, 4.81]	2007
Jung, 2010	9	62	2	5	3.4%	0.25 [0.04, 1.74]	2010
Jang, 2012	28	148	3	13	5.0%	0.78 [0.20, 3.01]	2012
Kim, 2013	15	182	3	11	4.8%	0.24 [0.06, 1.00]	2013
Spitaleri, 2013	14	137	6	35	6.2%	0.55 [0.19, 1.55]	2013
Ramakant, 2013	33	94	19	56	7.7%	1.05 [0.52, 2.11]	2013
Xiao, 2015	21	118	0	9	1.9%	4.19 [0.23, 74.78]	2015
Narayanakar, 2015	35	99	13	63	7.5%	2.10 [1.01, 4.39]	2015
Yom, 2015	19	271	1	14	3.1%	0.98 [0.12, 7.90]	2015
Bellezza, 2016	12	53	0	9	1.9%	5.72 [0.31, 105.40]	2016
Matos, 2017	14	40	3	12	4.7%	1.62 [0.38, 6.95]	2017
Choi, 2018	51	265	9	97	7.4%	2.33 [1.10, 4.94]	2018
Zhou, 2018	50	378	4	26	6.0%	0.84 [0.28, 2.53]	2018
Total (95% CI)		**2926**		**631**	**100.0%**	**1.05 [0.67, 1.63]**	
Total events	442		97				

Heterogeneity: Tau² = 0.55; Chi² = 48.20, df = 21 (P = 0.12); I² = 56%
Test for overall effect: Z = 0.20 (P = 0.84)
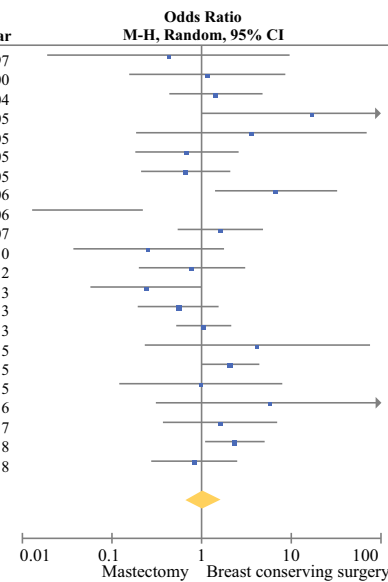
FIG. 2 **a** Forest plot showing the pooled odds ratios (ORs) of local recurrence (LR) by age. All studies used 40 years as the cutoff except for Wei et al.[62] (35 years) and Zhou et al.[18] (38 years). **b** Forest plot showing the pooled ORs of LR by tumor size (> 5 vs. ≤ 5 cm) except for Kim et al.[15] (4 cm). **c** Forest plot showing the pooled ORs of LR by surgery type (breast-conserving surgery vs. mastectomy). **d** Forest plot showing the pooled ORs of LR by surgical margin (positive vs. negative). The surgical margin width in each study was marked in the footnote. The study without a footnote did not mention the margin width in the article. *These studies (n = 14) defined a positive margin as a tumor present on the surgical margin. †These studies (n = 3) defined a positive margin as a tumor present on the surgical margin or less than 1 mm from the surgical margin. ‡This study (n = 1) defined a positive margin as a tumor present on the surgical margin or less than 0.1 mm from the surgical margin. #In Spitaleri et al.[20] three events (20 altogether) were not LR. One case had recurrence in the breast and axilla, and two cases had distant metastases

for malignant PTs but not for benign and borderline PTs, suggesting that the PT grade might provide important information in these aspects.

Emerging evidence suggests that a positive surgical margin of benign PTs is not related to LR and can be treated conservatively.

d Surgical margin
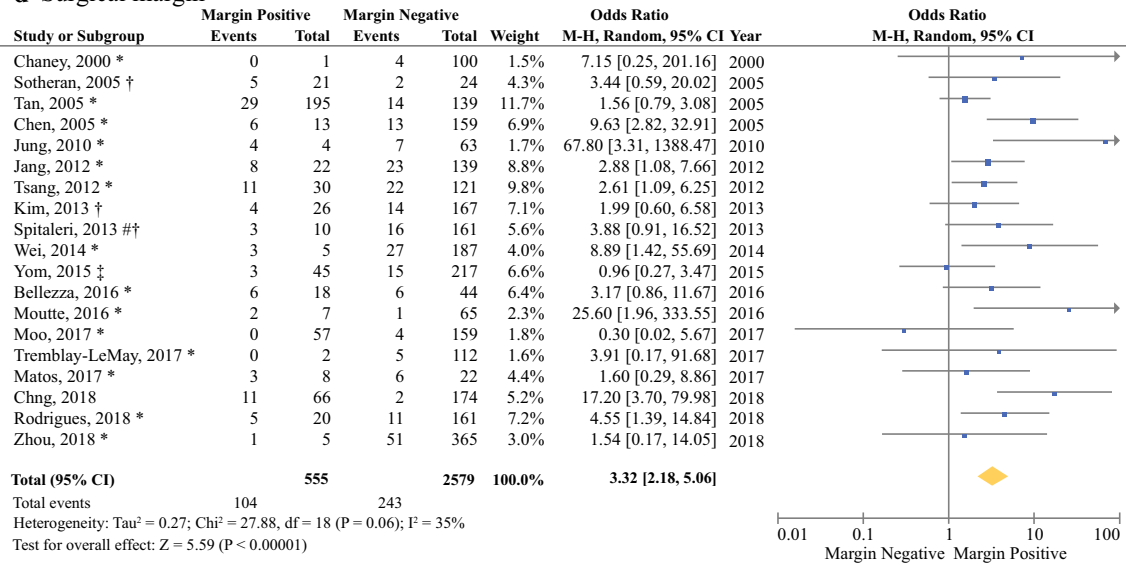
Study or Subgroup	Margin Positive Events	Total	Margin Negative Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Chaney, 2000 *	0	1	4	100	1.5%	7.15 [0.25, 201.16]	2000
Sotheran, 2005 †	5	21	2	24	4.3%	3.44 [0.59, 20.02]	2005
Tan, 2005 *	29	195	14	139	11.7%	1.56 [0.79, 3.08]	2005
Chen, 2005 *	6	13	13	159	6.9%	9.63 [2.82, 32.91]	2005
Jung, 2010 *	4	4	7	63	1.7%	67.80 [3.31, 1388.47]	2010
Jang, 2012 *	8	22	23	139	8.8%	2.88 [1.08, 7.66]	2012
Tsang, 2012 *	11	30	22	121	9.8%	2.61 [1.09, 6.25]	2012
Kim, 2013 †	4	26	14	167	7.1%	1.99 [0.60, 6.58]	2013
Spitaleri, 2013 #†	3	10	16	161	5.6%	3.88 [0.91, 16.52]	2013
Wei, 2014 *	3	5	27	187	4.0%	8.89 [1.42, 55.69]	2014
Yom, 2015 ‡	3	45	15	217	6.6%	0.96 [0.27, 3.47]	2015
Bellezza, 2016 *	6	18	6	44	6.4%	3.17 [0.86, 11.67]	2016
Moutte, 2016 *	2	7	1	65	2.3%	25.60 [1.96, 333.55]	2016
Moo, 2017 *	0	57	4	159	1.8%	0.30 [0.02, 5.67]	2017
Tremblay-LeMay, 2017 *	0	2	5	112	1.6%	3.91 [0.17, 91.68]	2017
Matos, 2017 *	3	8	6	22	4.4%	1.60 [0.29, 8.86]	2017
Chng, 2018	11	66	2	174	5.2%	17.20 [3.70, 79.98]	2018
Rodrigues, 2018 *	5	20	11	161	7.2%	4.55 [1.39, 14.84]	2018
Zhou, 2018 *	1	5	51	365	3.0%	1.54 [0.17, 14.05]	2018
Total (95% CI)		**555**		**2579**	**100.0%**	**3.32 [2.18, 5.06]**	
Total events	104		243				

Heterogeneity: Tau² = 0.27; Chi² = 27.88, df = 18 (P = 0.06); I² = 35%
Test for overall effect: Z = 5.59 (P < 0.00001)

FIG. 2 continued

TABLE 3 Associations between pathologic parameters and local recurrence (LR)

Pathologic parameters	No. of studies	No. of patients	OR	95% CI	p value[a]	χ^2	df	I^2, %	p value[a]	References
Mitoses ($\geq$ 10 vs. < 10)[b]	8	1741	2.89	1.40–5.97	**0.01**	0.71	7	71	**< 0.01**	15,18,19,35,43,49,58,66
Tumor border (infiltrative vs. pushing)	7	1409	2.79	1.43–5.46	**< 0.01**	0.49	6	66	**< 0.01**	13,15,18,35,43,46,66
Stromal cellularity (moderate/severe vs. mild)	8	1632	2.63	1.58–4.39	**< 0.01**	0.30	7	59	**0.02**	15,18,35,43,46,49,58,66
Stromal atypia (severe vs. mild/absent)	8	1654	2.32	1.08–4.96	**0.03**	0.72	7	64	**0.03**	15,18,28,35,43,49,58,66
Stromal overgrowth (severe vs. mild/absent)	10	1717	2.04	1.03–4.04	**0.04**	0.72	9	64	**< 0.01**	11,15,20,28,35,43,46,49,58,66
Tumor necrosis (positive vs. negative)	5	1180	2.00	1.17–3.40	**0.01**	NA	4	0	0.62	18,20,35,43,66

OR odds ratio, *CI* confidence interval

[a]Statistically significant results are shown in bold

[b]We compared $\geq$ 10 versus < 10 and $\geq$ 5 versus < 5 and found similar negative results

In our previous study, we reported that the LR risks were similar between benign PT patients who underwent ultrasound-guided vacuum-assisted biopsy (UGVAB) (assumed to have no assurance of a clear surgical margin) and those who had complete excision.[51] This study was acknowledged as evidence in a recent international consensus conference on lesions of uncertain malignant potential in the breast (B3 lesions).[73] More studies[48,74–76] confirmed that benign PTs might be treated conservatively, with close follow-up evaluation and timely re-excision of any potential recurrence. Taken together, these findings

suggest that whether a negative margin should be strictly obtained for benign PTs is open for discussion. The current evidence is obviously insufficient for concluding that a negative margin is dispensable for benign and borderline PTs, considering the limited number of studies included in the subgroup analysis. A cost-effective analysis of revision surgery for benign PTs with positive margins would be helpful, and further study is needed to investigate this issue.

The role of radiation therapy (RT) as a local control method for PTs remains highly debated. The NCCN

guideline cautions that RT for those additional recurrence would create significant morbidity.

In the current study, we did not assess RT as a risk factor due to the limited data. A recent meta-analysis[77] showed that RT significantly reduced the risk of LR. However, the validity of this outcome needs to be confirmed because that study included some literature with inconsistent events (disease-free survival instead of LR). An analysis of the Surveillance, Epidemiology, and End Results (SEER) data, including 1974 malignant PTs, also reported that although patients with more adverse prognostic factors underwent postoperative RT, the RT groups were not inferior to the non-RT group in terms of cancer-specific survival.[78] However, other studies have reported no protective effect of RT on LR.[15,79] More studies are warranted for further exploration of this issue.

Pathologists use various pathologic parameters to determine PT grades.[67] Tan et al.[30] proposed a nomogram using the surgical margin, atypia, mitoses, and stromal overgrowth to predict clinical outcomes. In addition to these factors, we found other risk factors for LR including the tumor border, stromal cellularity, and tumor necrosis. Pathologists and surgeons also should pay attention to these aspects.

Our meta-analysis had some limitations. First, this meta-analysis relied on retrospective studies, so selection bias cannot be excluded. Second, the sample size in the analysis of LR risk factors was relatively small, which limited the level of evidence. Finally, the follow-up period varied in each study. Therefore, we applied multiple strategies and strict criteria to evaluate the methodologic quality of the included studies.

CONCLUSIONS

The risk of LR was significantly increased from benign to borderline to malignant PTs. Mitoses, tumor border, stromal cellularity, stromal atypia, stromal overgrowth, tumor necrosis, type of surgery, and surgical margin status may be risk factors for LR. Different management strategies could be considered for different PT grades.

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