Breast cancer recurrence after immediate and delayed postmastectomy breast reconstruction—A systematic review and meta-analysis

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BACKGROUND: Oncological safety of different types and timings of PMBR after breast cancer remains controversial. Lack of stratified risk assessment in literature makes current clinical and shared decision-making complex. This is the first systematic review and meta-analysis to evaluate differences in oncological outcomes after immediate versus delayed postmastectomy breast reconstruction (PMBR) for autologous and implant-based PMBR separately. METHODS: A systematic literature search was performed in MEDLINE, Cochrane Library, and Embase. The Cochrane Collaboration Handbook and Meta-analysis Of Observational Studies in Epidemiology checklist were followed for data abstraction. Variability in point estimates attributable to heterogeneity was assessed using ²-statistic. (Loco)regional breast cancer recurrence rates, distant metastasis rates, and overall breast cancer recurrence rates were pooled in generalized linear mixed models using random effects.

RESULTS: Fifty-five studies, evaluating 14,217 patients, were included. When comparing immediate versus delayed autologous PMBR, weighted average proportions were: 0.03 (95% confidence interval [CI], 0.02–0.03) versus 0.02 (95% CI, 0.01–0.04), respectively, for local recurrences. 0.02 (95% CI, 0.01–0.03) versus 0.02 (95% CI, 0.01–0.03) for regional recurrences, and 0.04 (95% CI, 0.03–0.06) versus 0.01 (95% CI, 0.00–0.03) for locoregional recurrences. No statistically significant differences in weighted average proportions for local, regional and locoregional recurrence rates were observed between immediate and delayed autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrences after autologous PMBR, and of all outcome measures after implant-based PMBR.

CONCLUSIONS: Delayed autologous PMBR leads to similar (loco)regional breast cancer recurrence rates compared to immediate autologous PMBR. This study highlights the paucity of strong evidence on breast cancer recurrence after specific types and timings of PMBR. Cancer 2022;128:3449-3469. © 2022 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

LAY SUMMERY:

- Oncologic safety of different types and timings of postmastectomy breast reconstruction (PMBR) remains controversial.
- Lack of stratified risk assessment in literature makes clinical and shared decision-making complex.
- This meta-analysis showed that delayed autologous PMBR leads to similar (locoregional) recurrence rates as immediate autologous PMBR. Data did not allow comparing weighted average proportions of distant metastases and total breast cancer recurrence after autologous PMBR, and of all outcome measures after implant-based PMBR.
- Based on current evidence, oncological concerns do not seem a valid reason to withhold patients from certain reconstructive timings or techniques, and patients should equally be offered all reconstructive options they technically qualify for.

KEYWORDS: autologous, breast cancer, breast neoplasm, breast reconstruction, implant, metastasis, oncological safety, recurrence.

INTRODUCTION

Advances in early detection and treatment of breast cancer have improved breast cancer survival and shifted focus toward optimizing quality of life.¹ In this context, an increase in requests for postmastectomy breast reconstruction (PMBR) has been observed to preserve breast contour and function.² Autologous tissue, breast implants, or a combination, can be used to optimize quality of life. In this context, an increase in requests for postmastectomy breast reconstruction (PMBR) has been observed to preserve breast contour and function.

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for PMBR, either in an immediate or delayed fashion. Because of logistical challenges, concerns about delays in adjuvant treatment, and concerns of impaired outcomes of PMBR in combination with adjuvant radiotherapy, breast reconstruction is often performed in a delayed fashion. Still, immediate PMBR is considered superior in terms of patient satisfaction, costs, hospitalization and psychological benefits and as such, hospitals are increasingly offering immediate PMBR.

The growing application of PMBR has raised new concerns regarding long-term oncological safety. According to the concept of tumor dormancy, breast cancer patients might harbor dormant micrometastases that can be activated by stressors, such as extensive (reconstructive) surgery, thereby inducing recurrence and metastasis. Also, reconstructed breasts might mask recurrent tumors on radiological imaging.

In the absence of well-known landmark studies, the oncological safety of different types and timings of PMBR remains controversial. Isern and colleagues reported higher breast cancer recurrence rates after delayed PMBR than after mastectomy only, whereas others were not able to confirm this increased risk. Moreover, different relapse patterns were described, such as a higher 18-month peak in relapses following delayed versus no reconstruction, and after autologous versus implant-based reconstruction.

There is a paucity of studies comparing differences in oncological outcomes after immediate versus delayed PMBR for autologous and implant-based reconstructions separately. Making this distinction is important, because surgical impact, indications, and patient selection differ between autologous and implant-based reconstructions, and the same applies to immediate versus delayed reconstructions.

The abundance of inconclusive literature on breast reconstructive surgery makes current clinical decision-making and clear patient education complex. As such, contemporary decision-making remains based on expert consensus rather than scientific clinical evidence, subsequently leading to unequal access to reconstructive options. A well conducted up-to-date systematic review and meta-analysis (SR/MA) may provide more insight into this much-debated issue and support clinical and shared decision-making. Therefore, with this SR/MA, we aim to investigate whether delayed PMBR leads to different (loco)regional recurrence, distant metastasis, and overall recurrence rates than immediate PMBR in patients with primary breast cancer. Because of differences in nature and indications of implant-based and autologous breast reconstructive techniques, this question was evaluated separately for autologous and implant-based breast reconstruction.

MATERIALS AND METHODS
This SR/MA was registered in PROSPERO (CRD4202 0141137).

Search strategy
A comprehensive systematic literature search was performed following the Cochrane Collaboration Handbook and the Meta-analysis Of Observational Studies in Epidemiology checklist in MEDLINE (via PubMed), Embase and the Cochrane Library from inception to November 19, 2020 (Fig. 1). The search strategy was designed by three authors (C.A.B., A.D., and A.B.) and two hospital librarians (Nienke van der Werf and Carla Sloof-Enthoven), and included three components: “breast cancer,” “breast reconstruction,” and “oncological outcome” (Table S1). Duplicate articles were removed.

Study selection
Two authors (C.A.B. and M.I.) independently screened all articles for title and abstract. If title and abstract were ambiguous, the full-text article was reviewed. Authors were blinded for each other’s results until the screening process was completed. Subsequently, two independent authors (C.A.B. and M.I.) screened full-texts to select articles for inclusion in the SR/MA.

Original articles including patients >18 years old and reporting oncological outcomes (i.e., “local,” “regional,” “locoregional” or “total breast cancer recurrences,” and “distant metastasis”) after PMBR in patients with breast cancer were included. Because of the scarcity of randomized controlled trials, prospective and retrospective observational studies were included. Comparative studies with only one study arm meeting in- and exclusion criteria were included. Exclusion criteria included (1) other publication types (i.e., isolated abstracts, case reports, preclinical studies, reviews, meta-analyses, practical summary’s, guidelines, editorials, communications, correspondence, discussions, unrelated, duplicated, conference, overlapping data, authors response theses, books, and letters), (2) animal studies, (3) non-English or non-Dutch language articles, (4) studies published before 2000, (5) studies including cohorts with <50 patients, (6) studies with a mean follow-up <24 months or unknown follow-up, (7) studies including patients with PMBR after initial breast-conserving surgery or prophylactic mastectomy, and (8) studies including patients with distant metastasis at time of diagnosis or PMBR, and breast cancer recurrence before PMBR. Nonavailable full-text articles (9) were also excluded. In case of overlapping cohorts,
either the largest cohort or the cohort with the most suitable study design was included. A cross-refer- ence check was performed among included articles and ex- cluded reviews for additional studies meeting the inclu- sion criteria.

**Missing data**
All corresponding authors of articles reporting aggregated data on recurrences or metastases for immediate and de- layed or implant-based and autologous PMBR were con- tacted to request data for each group separately.

**Quality assessment and data extraction**
The quality of studies and risk of bias was evaluated with the Methodological Index for NOn-Randomized Studies, which is designed to critically appraise prospective and ret- rospective studies, as well as comparative and noncompar- ative studies. The maximum score for noncomparative studies is 16 and 24 for comparative studies. A higher total score corresponds with less risk of bias.

Data extraction was performed by two independent authors (C.A.B. and M.I.) using a standardized form that was pilot-tested and optimized accordingly. Extracted
FIGURE 2. Forest plots of local, regional, locoregional, distant, and total breast cancer recurrences after immediate and delayed autologous breast reconstruction. The first column shows the included studies by year of publication and first author. The second and third columns show the total number of recurrences and the total study population, respectively. The fourth column shows the recurrence rates with 95% CIs of each study. On the right, each study corresponds to a red square centered at the point estimate (i.e., recurrence rate) with black horizontal lines indicating the 95% CI. Powerful studies (i.e., studies with more participants) have a narrower 95% CI. The overall weighted recurrence rates are represented by the black diamonds. The width of the diamond represents the 95% CI for the overall weighted recurrence rate. The vertical lines highlight study-specific deviations from the overall weighted recurrence rates. 95% CI indicates 95% confidence interval; 95% CI GLMM, 95% confidence interval generalized linear mixed models; DMR, delayed breast reconstruction; df, degrees of freedom; GLMM, generalized linear mixed models; IBR, immediate breast reconstruction; P, p value. (A) Forest plot of local recurrences after immediate and delayed autologous breast reconstruction. (B) Forest plot of regional recurrence after immediate and delayed autologous breast reconstruction. (C) Forest plot of locoregional recurrence after immediate and delayed autologous breast reconstruction. (D) Forest plot of distant metastasis after immediate and delayed autologous breast reconstruction. (E) Forest plot of total breast cancer recurrence after immediate and delayed autologous breast reconstruction.

Data included study design, patient characteristics, interventions, and outcomes (Tables 2–4). Outcomes of interest were local, regional, locoregional, distant and overall breast cancer recurrence and expressed as the proportion of patients experiencing recurrence. Overall breast cancer recurrence was defined as the sum of all (loco)regional recurrences and distant metastases.

Discordances in study selection, quality assessment, and data extraction were resolved by discussion by two authors (C.A.B. and M.I.). In case of disagreement, a third author (D.A.Y.- A.) was involved in reaching consensus.

Data analysis
For all studies, one or more of the primary outcomes of interest were reported. Proportions of recurrence and distant metastasis were pooled in a generalized linear mixed model (GLMM) and presented as forest plots. Publication bias was considered acceptable if the distribution of studies was symmetrical on visual inspection of the funnel plots. The variability in point estimates attributable to heterogeneity was assessed using the Higgins’s and Thompson’s $I^2$-statistic, which was tolerable if $I^2$ values were low or moderate (<75%).17 Based on $I^2$ values, analyses for the primary outcomes were conducted using random effects models. Weighted averages were reported as proportions with 95% confidence intervals (95% CI). Variances of distribution of true proportions among subgroups (between-study variances) were reported using $T^2$ values. When no variance between studies is observed, $T^2$ is low or 0.18 Differences in weighted average proportions after delayed versus immediate breast reconstruction were evaluated among subgroups by comparing 95% CIs. In case of overlapping 95% CIs, differences were not considered statistically significant. Statistical analyses were performed in the R software environment (R Foundation of Statistical Computing).

RESULTS

Search results and synthesis of evidence
After removing 1277 duplicates, the literature search yielded 3049 unique studies (Fig. 1). After title and abstract screening, full texts of 371 studies were assessed for eligibility. Finally, 48 studies4,9,11,13,19–62 met the inclusion criteria. Additional data was requested for 65 studies (Table S2) of whom seven (10.8%)6,60,63–68 provided data, enabling inclusion of these studies in analyses. In total, 55 studies4,8,9,11,13,19–68 were selected for qualitative synthesis (Tables 2–4). Quantitative synthesis included 37 studies4,8,9,11,13,19–21,30,39–47,50–52,56,58,59,62–65,67,68 on autologous PMBR (Figs. 2A-E; Table S3a) and 28 studies20,31–38,41–43,46–49,53–55,57–61,64,66–68 on implant-based PMBR (Figs. 3A–E; Table S3b).

Study characteristics and quality of evidence
All included studies were published between February 200343 and October 202068 (Table 2). Among the 55 studies, 48 studies (87.3%)4,8,9,11,13,19–23,25–32,34,36,38–41,43–54,56–58,60–68 were retrospective and seven (12.7%)24,33,35,37,42,55,59 were prospective. The quality of included studies ranged from 6 to 12 points for noncomparative studies, and from 10 to 20 points for comparative studies (Table 1).

Study population
The 55 studies evaluated 14,452 patients, including 12,480 PMBRs performed in an immediate setting, 1852 in a delayed setting, and for 33765 the setting was unclear (Tables 2–4). Median sample size per study was 138 patients (interquartile range, 77–249). Mean/median age ranged from 33 to 53 years old. Mean/median follow-up time ranged from 27 to 146 months. The majority of patients (n = 11,429, 80.4%) were diagnosed with invasive breast cancer.

Immediate versus delayed autologous PMBR
A total of 31 studies3,4,9,13,19,21–30,39,40,42,44,45,47,50–52,56,59,62–65,67,68 included local recurrence as an outcome.
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(2) $\chi^2 = 51.7\%$ [95% CI, 27.9\%–67.6\%], 28 of which $4.2 \pm 30.49, 42.44, 44.47, 50.52, 56.92, 65.67, 68.75$ ($T^2 = 0.29$) reported on immediate autologous post-mastectomy breast reconstruction (I-ABR) and five studies ($T^2 = 0.24$) on delayed autologous post-mastectomy breast reconstruction (D-ABR). In the I-ABR group, 163
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FIGURE 3. Forest plots of local, regional, locoregional, distant and total breast cancer recurrences after immediate and delayed implant-based breast reconstruction. The first column shows the included studies by year of publication and first author. The second and third columns show the total number of recurrences and the total study population, respectively. The fourth column shows the recurrence rates with 95% CIs of each study. On the right, each study corresponds to a red square centered at the point estimate (i.e., recurrence rate) with black horizontal lines indicating the 95% CI. Powerful studies (i.e., studies with more participants) have a narrower 95% CI. The overall weighted recurrence rates are represented by the black diamonds. The width of the diamond represents the 95% CI for the overall weighted recurrence rate. The vertical lines highlight study-specific deviations from the overall weighted recurrence rates. 95% CI indicates 95% confidence interval; 95% CIGLM, 95% confidence interval generalized linear mixed models; DBR, delayed breast reconstruction; df, degrees of freedom; GLMM, generalized linear mixed model; IBR, immediate breast reconstruction; P, p value. (A) Forest plot of local recurrences after immediate implant-based breast reconstruction. No studies were available on local recurrences after delayed implant-based breast reconstruction. (B) Forest plot of regional recurrences after immediate implant-based breast reconstruction. No studies were available on regional recurrences after delayed implant-based breast reconstruction. (C) Forest plot of locoregional recurrence after immediate and delayed implant-based breast reconstruction. (D) Forest plot of distant metastasis after immediate and delayed implant-based breast reconstruction. (E) Forest plot of total breast cancer recurrences after immediate and delayed implant-based breast reconstruction.
of 6,249 patients (2.6%) developed local recurrence, and in the D-ABR group 22 of 1,037 patients (2.1%) developed local recurrence (Table S3a). The weighted average proportion for local recurrence in the I-ABR group was 0.03 (95% CI, 0.02–0.03), and 0.02 (95% CI, 0.01–0.04) in the D-ABR group.

| Abbreviation: MINORS, methodological index for non-randomized studies. |
| Note: Each item was scored 0–2 points: 0 indicates that this item was not reported in the article, 1 indicates that it was reported, but inadequately, and 2 indicates that it was reported adequately. A higher total score corresponds with less risk of bias. Green, 2 points; yellow, 1 point; red, 0 points. |
### TABLE 2. Study Characteristics And Baseline Characteristics Of Included Study Populations

| Year | First author | Country       | Journal                          | Study design | No. of patients | No. of breasts | Age (range), years | Follow-up (range), months | Reconstructive method               |
|------|--------------|---------------|----------------------------------|--------------|-----------------|----------------|-------------------|----------------------------|-------------------------------------|
| 2014 | Adam         | Sweden        | Eur J Surg Oncol                | Re           | 67              | 69             | 49.3 (24–74)      | 36.3 (4–162)                | Immediate, implant-based            |
| 2018 | Adam         | Sweden        | Br J Surg                       | Re           | 250             | 254            | 48.2 (25–67)      | 89.6 (4–214)                | Immediate, implant-based            |
| 2019 | Bjöhle       | Sweden        | Radiother Oncol                 | Re           | 128             | 128            | 46.2 (21–68)      | 69.6 (1–90)                 | Immediate, implant-based            |
| 2006 | Caruso       | Italy         | Eur J Surg Oncol                | Re           | 50              | 51             | 42.0 (28–68)      | 66.6 (9–140)                | Immediate, implant-based            |
| 2018 | Chen         | Taiwan        | Ann Plast Surg                  | Re           | 111             | 111            | 40.5 (SD = 7.5)   | 85.3 (91.0)                 | Immediate, implant-based            |
| 2017 | Cont         | Italy         | Breast Cancer Res Treat         | Re           | 518             | 518            | NR                | 33.3 (NR)                  | Immediate, implant-based            |
| 2016 | Dilléka      | Norway        | Breast Cancer Res Treat         | Re           | 312             | 312            | 48.0 (NR)         | 137.0 (NR)                 | Delayed, autologous               |
| 2017 | Du           | China         | Sci Rep                         | Pr           | 157             | 157            | NR                | 74.0 (62–111)              | Immediate, implant-based            |
| 2020 | Early        | United States of America | Clin Breast Cancer | Re          | 337             | 337            | NR (34–70)        | 45.4 (NR)                  | Immediate and delayed, autologous   |
| 2011 | Eriksen      | Sweden        | Breast Cancer Res Treat         | Re           | 300             | 300            | 48.0 (23–70)      | 144.0 (48–216)             | Immediate, implant-based            |
| 2016 | Fujimoto     | Japan         | Eur J Plast Surg                | Re           | 136             | 144            | 42.0 (24–63)      | 75.0 (51–129)              | Immediate, autologous             |
| 2018 | Geers        | Belgium       | BMC Cancer                      | Re           | 485             | 485            | 47.0 (24–71)      | 76.0 (4–152)                | Immediate and delayed, autologous   |
| 2010 | Ha           | South-Korea   | Am J Surg                       | Re           | 225             | 225            | 50.0 (25–76)      | 49.0 (NR)                  | Immediate, autologous and implant-based |
| 2008 | Hölmich      | Denmark       | Ann Plast Surg                  | Re           | 580             | 580            | 47.0 (24–72)      | 121.0 (12–155)             | Delayed, implant-based            |
| 2006 | Huang        | China         | Plast and Reconstr Surg         | Re           | 82              | 83             | 42.7 (27–58)      | 40.0 (24–74)               | Immediate, autologous             |
| 2011 | Isen         | Sweden        | Br J Surg                       | Re           | 125             | 125            | 45.4 (SD = 7.8)   | 146.0 (NR)                 | Delayed, autologous               |
| 2010 | Kim          | South-Korea   | Ann of Surg                     | Re           | 520             | 520            | 42.0 (35–50)      | 63.0 (NR)                  | Immediate, autologous             |
| 2012 | Kim          | South-Korea   | World J Surg Oncol              | Re           | 65              | 65             | 48.4 (21–74)      | 34.0 (1.6–89.9)            | Immediate, autologous             |
| 2016 | Lee          | Taiwan        | PLoS ONE                        | Re           | 213             | 213            | 44.8 (26–60)      | 85.2 (80)                  | Immediate, autologous             |
| 2020 | Lee          | South-Korea   | Br J Surg                       | Pr           | 438             | 438            | 43.1 (SD = 7.4)   | 82.0 (13–131)              | Immediate, autologous and implant-based |
| 2018 | Lee          | South-Korea   | Medicine (Baltimore)            | Re           | 1032            | 1032           | 48.1 (23–90)      | 94.4 (81–220.2)            | Immediate, autologous             |
| 2019 | Lee          | South-Korea   | Asia J Med                      | Re           | 118             | 118            | 33.0 (23–35)      | 86.7 (NR)                  | Immediate, autologous             |
| 2012 | Lee          | South-Korea   | Arch Plast Surg                 | Pr           | 1000            | 1000           | 42.2 (22–68)      | 56.4 (3–93)                | Immediate, autologous             |
| 2013 | Liang        | Taiwan        | World J Surg Oncol              | Re           | 249             | 249            | 41.0 (22–62)      | 53.0 (24–181)              | Immediate, autologous             |
| 2010 | Lim          | South-Korea   | World J Surg Oncol              | Re           | 112             | 125            | 53.0 (24–69)      | 64.0 (5–111)               | Immediate, autologous             |
| 2017 | Maalouf      | Canada        | Ann Chir Plast Est              | Re           | 62              | 62             | Immediate: 50.0 (SD = 9.5) | Immediate: 32.0 (11–67) | Immediate and delayed, autologous |
| 2008 | McCarthy      | United States of America | Plast Reconstr Surg | Re          | 309             | 309            | 46.8 (25.6–73.3)  | 68.4 (2.4–111.6)           | Immediate, implant-based            |
| 2020 | Metere       | Italy         | Medicina (Kaunas)               | Re           | 894             | 894            | 47.5 (22–76)      | 41.2 (15.7–101)            | Immediate, implant-based            |
| 2010 | Min          | South-Korea   | Breast J                        | Re           | 120             | 120            | 40.7 (26–61)      | 39.2 (SD = 15.8)           | Immediate, autologous             |
| 2013 | Munhoz       | Brazil        | Breast Canc Res Treat           | Re           | 106             | 114            | 51.4 (33–78)      | 65.8 (6–130)               | Immediate, implant-based            |
| 2017 | Murphy       | United States of America | Am J Surg                      | Pr           | 226             | 240            | 48.5 (43–54)      | 34.0 (NR)                  | Immediate, implant-based            |
| 2005 | Mustonen     | Finland       | Scand J Surg                    | Re           | 56              | 56             | SSM = 46.8 (SD = 8.2) | SSM = 43.2 (SD = 9.6) | Immediate, autologous             |
| 2015 | Narui        | Japan         | Eur J Surg Oncol                | Re           | 201             | 205            | 42.2 (23–64)      | 36.0 (NR)                  | Immediate, autologous             |
| Year | First author | Country | Journal | Study design | No. of patients | No. of breasts | Age (range), years | Follow-up (range), months | Reconstructive method |
|------|--------------|---------|---------|--------------|----------------|---------------|-------------------|--------------------------|------------------------|
| 2012 | Nava35       | Italy   | Breast  | Pr           | 58             | 59            | NR                | 36 (24–84)              | Immediate, implant-based |
| 2014 | Ota36        | Japan   | Clin Breast Cancer | Re        | 133            | 133           | 46 (27–49)        | 47 (NR)                 | Immediate, implant-based |
| 2020 | Ozmen61      | Turkey  | World J Surg Oncol | Re        | 75             | 75            | 42 (24–78)        | 56 (14–116)             | Immediate, implant-based |
| 2016 | Park40       | South-Korea | J Breast Cancer | Re       | 189            | 189           | 41.96 (SD = 80.8) | 65.6 (10–132)           | Immediate, implant-based |
| 2020 | Parvez90     | Canada  | Clin Breast Cancer | Re        | 162            | 173           | 47.9 (SD = 11.2)  | 27 (5–68)               | Immediate, implant-based |
| 2012 | Patterson10   | United States of America | Ann Surg Oncol | Re      | 390            | 390           | 49.5 (SD = 8.3)   | 69.2 (24.1–134.4)       | Immediate, implant-based |
| 2011 | Reddy41      | United States of America | Ann Plast Surg | Re      | 494            | 494           | 47.8 (23.9–72.2)  | 54 (NR)                 | Immediate, autologous and implant-based |
| 2012 | Romics42      | Scotland | Br J Surg | Pr       | 207            | 207           | 49 (26–68)        | 119 (14–163)            | Immediate, implant-based |
| 2016 | Sakamoto57   | Japan   | Breast Cancer | Re       | 404            | 421           | 40 years: 92 < 40 years: 329 | 61 (7.2–139)           | Immediate, implant-based |
| 2008 | Scholz52     | United States of America | Plast Reconstr Surg | Re  | 54             | 54            | 51.5 (31–69)      | 42 (12–108)             | Immediate, autologous |
| 2013 | Serra57      | Italy   | Plast Surg Int | Pr       | 155            | 155           | 37.5 (20–52)      | 47 (12–96)              | Immediate, implant-based |
| 2007 | Sno51        | Slovenia | Eur J Surg Oncol | Re  | 156            | 157           | 45.9 (26–68)      | 66 (18–277)            | Immediate, autologous and delayed, autologous |
| 2003 | Spieger43    | United States of America | Plast Reconstr Surg | Re  | 221            | 221           | 42 (24–81)        | 117.6 (72–156)         | Immediate, autologous and implant-based |
| 2016 | Tanos44      | United Kingdom | Plast Reconstr Surg | Glob Open | 88            | 88            | Implant-based: 48 (29–75) | Implant-based: 28.2 (NR) | Immediate, autologous and implant-based |
| 2008 | Ueda45       | Japan   | Surgery | Re       | 74             | 74            | 45.7 (NR)         | 50 (NR)                 | Immediate, autologous and implant-based |
| 2019 | Valente46     | United States of America | Am J Surg | Re      | 458            | 586           | 49 (26–85)        | 90.48 (65.64–144.96)    | Immediate, autologous and implant-based |
| 2007 | Vaughan57    | United States of America | Am J Surg | Re | 206            | 210           | Local recurrence: 41 (31–56) | 58.6 (13.1–132.5) | Immediate, autologous and implant-based |
| 2020 | Wu37         | South-Korea | Ann Surg Oncol | Re | 199            | 199           | 43 (20–65)        | 97 (39–186)             | Immediate, autologous and implant-based |
| 2020 | Wu38         | South-Korea | JAMA Surg | Re | 323            | 323           | 42 (23–72)        | 67 (17–125)             | Immediate, autologous and implant-based |
| 2020 | Yamada62     | Japan   | J Surg Res | Re | 239            | 239           | 44 (23–65)        | 73 (NR)                 | Immediate, autologous |

Abbreviations: NR, not reported; Pr, prospective; Re, retrospective; SCM, subcutaneous mastectomy; SD, standard deviation; SSM, skin-sparing mastectomy. 
aMean. 
bMedian.
### TABLE 3. Oncological Characteristics Of Included Study Populations

| Year | First author | AJCC stage (n) | T classification (n) | Histology (n) | ER (n) | PR (n) | Her2Neu (n) |
|------|--------------|----------------|---------------------|--------------|--------|--------|-------------|
| 2014 | Adam48       | NR             | Tis: NR T1: 37 T2: 14 T3: 3 T4: 1 Missing: 14 | In situ: 14 Invasive: 55 Missing: 0 | Positive: 44 Negative: 14 Missing: 11 | Positive: 40 Negative: 17 Missing: 12 | Positive: 44 Negative: 7 Missing: 18 |
| 2018 | Adam19       | NR             | Tis: 9 T1: 65 T2: 140 T3: 40 T4: 0 Missing: 0 | In situ: 9 Invasive: 219 Missing: 19 | Positive: 176 Negative: 61 Missing: 17 | Positive: 148 Negative: 75 Missing: 31 | Positive: 31 Negative: 89 Missing: 134 |
| 2019 | Bjöhle38     | NR             | Tis: 0 T1: 65 T2: 45 T3: 13 T4: 0 Missing: 5 | In situ: 0 Invasive: 128 Missing: 0 | Positive: 95 Negative: 32 Missing: 1 | NR | Positive: 20 Negative: 98 Missing: 0 |
| 2006 | Caruso31     | 0: 8 I: 24 II: 18 III: 1 | NR | In situ: 21 Invasive: 30 Missing: 0 | Positive: 37 Negative: 9 Missing: 5 | Positive: 32 Negative: 14 Missing: 5 | NR |
| 2018 | Chen32       | 0: 0 I: 6 II: 63 III: 42 Missing: 0 | T0–T1: 32 T2: 70 T3: 8 T4: 1 | NR | Positive: 78 Negative: NR Missing: NR | Positive: 74 Negative: NR Missing: NR | Positive: 23 Negative: 66 Null: 1 Missing: 21 |
| 2017 | Cont49       | NR             | NR | NR | Positive: 442 Negative: NR Missing: 11 | Positive: 404 Negative: NR Missing: 13 | Positive: 76 Negative: NR Missing: 100 |
| 2016 | Dillekâs9    | NR             | Tis: 0 T1: 190 T2: 91 T3: 22 T4: 2 | In situ: 0 Invasive: 312 Missing: 0 | Positive: 113 Negative: 44 Missing: 0 | NR | Positive: 53 Negative: 104 Missing: 0 |
| 2017 | Du33         | 0: 0 I: 36 II: 97 III: 24 | NR | In situ: 0 Invasive: 157 Missing: 0 | Positive: 113 Negative: 44 Missing: 0 | NR | Positive: 53 Negative: 104 Missing: 0 |
| 2020 | Early65      | NR             | NR | NR | Positive: 219 Negative: NR Missing: 26 | Positive: 219 Negative: NR Missing: 26 | Positive: 53 Negative: 104 Missing: 0 |
| 2011 | Eriksen54    | NR             | NR | NR | Positive: 219 Negative: NR Missing: 26 | Positive: 219 Negative: NR Missing: 26 | Positive: 53 Negative: 104 Missing: 0 |
| 2016 | Fujimoto21   | 0: 48 I: 35 II: 44 III: 7 | Tis: 48 T1: 42 T2: 36 T3: 8 | In situ: 48 Invasive: 488 Missing: 0 | Positive: 82 Negative: 26 Missing: 28 | NR | Positive: 20 Negative: 101 Missing: 15 |
| 2018 | Geers8       | I: 45 II: 206 III: 225 | NR | In situ: NR Invasive: 485 Missing: 0 | Positive: 374 Negative: 103 Missing: 8 | Positive: 374 Negative: 103 Missing: 8 | Positive: 92 Negative: 375 Missing: 18 |
| 2005 | Greenway64   | 0 - II | Tis: 27 T1: 123 T2: 75 T3–T4: 0 | NR | NR | NR | NR |
| Year | First author | AJCC stage (n) | T classification (n) | Histology (n) | ER (n) | PR (n) | Her2Neu (n) |
|------|--------------|----------------|---------------------|---------------|--------|--------|------------|
| 2020 | Ha38 | Implant-based/autologous: 0: 47/57 I: 100/82 II: 73/79 III: 27/31 Missing: 0 | NR | NR | Implant-based/autologous: Positive: 198/206 Negative: 49/43 Missing: 0/0 | Implant-based/autologous: Positive: 171/173 Negative: 76/76 Missing: 0/0 | Implant-based/autologous: Positive: 56/44 Negative: 174/193 Missing: 17/12 |
| 2008 | Hölmich20 | | T1: 370 T2–T4: 188 Missing: 22 | In situ: NR Invasive: 548 Missing: 32 | NR | NR | NR |
| 2006 | Huang22 | 0: 0 I: 4 II: 64 III: 14 | NR | Positive: 28 Negative: 48 Missing: 9 | Positive: 28 Negative: 48 Missing: 9 | NR |
| 2011 | Isern11 | NR | Tis: 0 T1: 60 T2: 60 T3: 5 T4: 0 Missing: 0 | In situ: 0 Invasive: 125 Missing: 0 | Positive: 105 Negative: 20 Missing: 0 | Positive: 23 Negative: 101 Missing: 1 |
| 2010 | Kim23 | 0: 84 I: 220 II: 176 III: 40 | NR | NR | Positive: 324 Negative: 180 Missing: 10 | NR | 0–2: 341 3: 158 Missing: 21 |
| 2012 | Kim29 | 0: 15 I: 29 II: 20 III: 1 | Tis: 15 T1: 30 T2: 20 T3–T4: 0 Missing: 0 | In situ: 15 Invasive: 50 Missing: 0 | NR | NR | NR |
| 2016 | Lee25 | 0: 0 I: 0 II: 121 III: 92 | Tis: 0 T1: 48 T2: 134 T3: 24 T4: 7 Missing: 0 | In situ: 0 Invasive: 213 Missing: 0 | Positive: 113 Negative: 83 Missing: 17 | Positive: 95 Negative: 19 Missing: 19 | |
| 2020 | Lee36 | 0: 116 I-Ill: 332 | Tis: 116 T1–T4: NR | In situ: 116 Invasive: 332 Missing: 0 | Positive: 341 Negative: 97 Missing: 0 | Positive: 320 Negative: 118 Missing: 0 | Positive: 169 Negative: 269 Missing: 0 |
| 2018 | Lee36 | 0: 164 I: 382 II: 399 III: 87 | NR | | Positive: 656 Negative: 338 Missing: 38 | Positive: 616 Negative: 378 Missing: 38 | Positive: 332 Negative: 644 Missing: 56 |
| 2019 | Lee37 | 0: 0 I: 54 II: 50 III: 14 | NR | In situ: 0 Invasive: 118 Missing: 0 | Positive: 72 Negative: 47 Missing: 0 | Positive: 61 Negative: 47 Missing: 0 | Positive: 47 Negative: 72 Missing: 0 |
| 2012 | Lee34 | 0: 173 I: 362 II: 371 III: 93 | NR | NR | Positive: 137 Negative: 112 Missing: 0 | Positive: 137 Negative: 112 Missing: 0 | NR |
| 2013 | Liang28 | 0: 0 I: 32 II: 132 III: 85 | Tis: 0 T1: 110 T2: 130 T3: 6 T4: 3 Missing: 0 | In situ: 0 Invasive: 249 Missing: 0 | Positive: 162 Negative: 22 Missing: 0 | Positive: 137 Negative: 112 Missing: 0 | NR |
| 2013 | Lindford13 | NR | Tis: 0 T1: 46 T2: 56 T3: 6 T4: 3 Missing: 1 | In situ: 0 Invasive: 112 Missing: 0 | Positive: 92 Negative: 20 Missing: 0 | Positive: 73 Negative: 39 Missing: 0 | Positive: 20 Negative: 80 Missing: 12 |

(Continued)
| Year  | First author | AJCC stage (n) | T classification (n) | Histology (n) | ER (n)                   | PR (n)                   | Her2Neu (n) |
|-------|--------------|----------------|----------------------|---------------|--------------------------|--------------------------|-------------|
| 2010  | Lim          | 0: 0           | T1: 13               | In situ: NR   | “Hormone receptor”:      | Positive: 26             | Negative: 57 |
|       |              | I: 0           | T2: 48               | Invasive: 87  | Positive: 65             | Negative: 22             | Negative: 22 |
|       |              | II: 8          | T3: 26               | Missing: 0    | Negative: 22             | Missing: 0               | Missing: 4  |
|       |              | III: 79        |                      |               |                          |                          |             |
| 2017  | Maalouf      | Immediate/delayed: 0: 1/0 | Immediate/delayed: | In situ: 1/0 | Immediate/delayed:       | Immediated/ delayed:     | Immediate/ delayed:     | Immediate/ delayed: |
|       |              | I: 5/9         | T1: 13               | Invasive: 29/32| Negative/missing:       | Positive: 17/22         | Negative/missing:     | Negative/missing:   |
|       |              | II: 16/12      | T2: 48               | Missing: 0/0  | Positive/missing:        | Negative/missing:        | Positive/missing:     | Negative/missing:   |
|       |              | III: 8/11      | T3: 26               | Missing: 0    |                          |                          | Negative/missing:     | Negative/missing:   |
| 2008  | McCarthy      | NR             | NR                   | In situ: 0    | Positive: 189            | Negative: 77            | Negative: 106         | Negative: 46     |
|       |              | I: 98          | Invasive: 309        | Missing: 0    | Positive: 157            | Negative: 106           | Negative: 106         | Negative: 46     |
|       |              | II: 164        |                      |               |                          |                          |                          |              |
|       |              | III: 47        |                      |               |                          |                          |              |
| 2020  | Metere       | NR             | NR                   | In situ: 0    | Positive: 205            | Negative: 30            | Negative: 46            | Positive: 18     |
|       |              | I-II: 75.2%    | Invasive: 662        | Negative: 22  | Positive: 729            | Negative: 165           | Negative: 823         | Negative: 0      |
|       |              | III: NR        | Other: 9             | Missing: 0    | Positive: 71             | Negative: 165           | Negative: 165         | Negative: 0      |
| 2010  | Min          | NR             | NR                   | In situ: 0    | Positive: 107            | Negative: 19            | Missing: 85            | Positive: 14     |
|       |              | I: 22          | Invasive: 98         | “Hormone receptor”: | Positive: 76      | Negative: 40            | Negative: 40          | Negative: 12     |
|       |              | II: 48         | Missing: 0           | “Hormone receptor”: | Positive: 40      | Negative: 40            | Negative: 40          | Negative: 12     |
|       |              | III: 31        |                     | “Hormone receptor”: | Missing: 4        |                           |                          | Negative/missing: |
|       |              | III: 13        |                     | “Hormone receptor”: |                         |                           |                          | Negative/missing: |
| 2013  | Munhoz       | NR             | NR                   | Tis: 0        | Positive: 205            | Negative: 30            | Negative: 46           | Positive: 18     |
|       |              |                 |                      | T1: 78        | Positive: 157            | Negative: 106           | Negative: 106         | Negative: 46     |
|       |              |                 |                      | T2: 28        |                          |                          |                          |              |
|       |              |                 |                      | T3–T4: 0      |                          |                          |                          |              |
| 2017  | Murphy       | NR             | NR                   | T0–Tis: 73    | Positive: 205            | Negative: 30            | Negative: 46           | Positive: 18     |
|       |              |                 |                      | T1: 109       | Positive: 157            | Negative: 106           | Negative: 106         | Negative: 46     |
|       |              |                 |                      | T2: 47        |                          |                          |                          |              |
|       |              |                 |                      | T3: 11        |                          |                          |                          |              |
|       |              |                 |                      | T4: 0         |                          |                          |                          |              |
| 2005  | Mustonen     | NR             | NR                   | Tis: 0        | Positive: 205            | Negative: 30            | Negative: 46           | Positive: 14     |
|       |              |                 |                      | T1: 78        | Positive: 157            | Negative: 106           | Negative: 106         | Negative: 46     |
|       |              |                 |                      | T2: 28        |                          |                          |                          |              |
|       |              |                 |                      | T3–T4: 0      |                          |                          |                          |              |
| 2015  | Naru         | NR             | NR                   | DCIS: 63      | Positive: 107            | Negative: 13            | Missing: 85            | Positive: 14     |
|       |              |                 |                      | Invasive: 168 | Negative: 107            | Negative: 13            | Missing: 85            | Positive: 14     |
|       |              |                 |                      | Other: 9      |                          |                          |                          |              |
| 2012  | Nava         | 0: 8           | Tis: 8               | In situ: 8    | Positive: 38             | Negative: 10            | Negative: 10          | Positive: 12     |
|       |              |                 |                      | T1: 35        | Positive: 38             | Negative: 10            | Negative: 10          | Positive: 12     |
|       |              |                 |                      | T2: 12        |                          |                          |                          |              |
|       |              |                 |                      | T3: 1         |                          |                          |                          |              |
|       |              |                 |                      | T4: 0         |                          |                          |                          |              |
| 2014  | Ota          | NR             | NR                   | Tis–T3: 128   | In situ: 20              | Positive: 114           | Negative: 19          | Positive: 15     |
|       |              |                 |                      | T4: 5         | “Hormone receptor”:      | Positive: 114           | Negative: 19          | Positive: 15     |
|       |              |                 |                      | Missing: 0    | “Hormone receptor”:      | Positive: 114           | Negative: 19          | Positive: 15     |
| 2020  | Ozmen        | 0: 0           | Tis: 0               | In situ: 0    | Positive: 129            | Negative: 60            | Negative: 89          | Positive: 55     |
|       |              |                 |                      | T1: 121       | Positive: 129            | Negative: 60            | Negative: 89          | Positive: 55     |
|       |              |                 |                      | T2: 52        |                          |                          |                          |              |
|       |              |                 |                      | T3: 13        |                          |                          |                          |              |
|       |              |                 |                      | T4: 3         |                          |                          |                          |              |
| 2016  | Park         | 0: 0           | Tis: 0               | In situ: 0    | Positive: 129            | Negative: 60            | Negative: 89          | Positive: 55     |
|       |              |                 |                      | T1: 121       | Positive: 129            | Negative: 60            | Negative: 89          | Positive: 55     |
|       |              |                 |                      | T2: 52        |                          |                          |                          |              |
|       |              |                 |                      | T3: 13        |                          |                          |                          |              |
|       |              |                 |                      | T4: 3         |                          |                          |                          |              |

**TABLE 3. Continued**
| Year | First author | AJCC stage (n) | T classification (n) | Histology (n) | ER (n) | PR (n) | Her2Neu (n) |
|------|--------------|----------------|---------------------|---------------|-------|--------|-------------|
| 2020 | Parvez56     | NR             | Tis: 31             | In situ: NR   | "Hormone receptor": Positive: 24 |
|      |              |                | T1: 83              | Invasive: 144 | Positive: 103 |
|      |              |                | T2: 51              | Missing: 31  | Positive: 103 |
|      |              |                | T3: 10              |                | Negative: 41  |
|      |              |                | T4: 0               |                | Missing: 31   |
| 2012 | Patterson50   | 0– II: 312     | NR                  | In situ: 100  | Positive: 215 |
|      |              | II: 70         |                     | Invasive: 254 | Positive: 193 |
|      |              | Missing: 0     |                     | Missing: 36  | Negative: 88  |
| 2011 | Reddy41      | 0: 119         | NR                  | In situ: NR   | Positive: 295 |
|      |              | I: 183         |                     | Invasive: 144 | Positive: 128 |
|      |              | II: 114        |                     | Missing: 0   | Negative: 90  |
|      |              | III: 43        |                     |               | Missing: 109  |
| 2012 | Romics42     | 0: 54          | Tis: 54             | In situ: 54  | Positive: 119 |
|      |              | I: 57          | T1: 94              | Invasive: 153 | Negative: 34  |
|      |              | II: 83         | T2: 52              | Missing: 0   | Missing: 54   |
|      |              | III: 13        | T3: 6               |               |               |
|      |              |                | T4: 1               |               |               |
|      |              |                | Missing: 0          |               |               |
| 2016 | Sakamoto57   | 0: 117         | NR                  | In situ: 117  | Positive: 333 |
|      |              | I: 149         |                     | Invasive: 304 | Negative: 71  |
|      |              | II: 141        |                     | Missing: 0   | Missing: 17   |
| 2008 | Scholz52     | 0: 23          | NR                  | In situ: 23  | Positive: 57  |
|      |              | I: 17          |                     | Invasive: 31  | Negative: 231 |
|      |              | II: 14         |                     | Missing: 0   | Missing: 133  |
| 2013 | Serra37      | NR             | Tis: 23             | In situ: 23  | Positive: 84  |
|      |              |                | T1: 36              | Invasive: 132 | Negative: 67  |
|      |              |                | T2: 96              | Missing: 0   | Missing: 6    |
|      |              |                | T3–T4: 0            | Missing: 3   |               |
| 2007 | Snoj51       | NR             | Tis: 0              | In situ: 0   | Positive: 99  |
|      |              |                | T1: 78              | Invasive: 157 | Negative: 53  |
|      |              |                | T2: 61              | Missing: 0   | Missing: 5    |
|      |              |                | T3: 15              |               |               |
|      |              |                | Missing: 3          |               |               |
| 2003 | Spiegel & Butler43 | NR | NR | In situ: 44 | Positive: 44 |
|      |              |                |                     | Invasive: 177 | Negative: 0   |
|      |              |                |                     | Missing: 0   |               |
| 2016 | Tanos44      | 0–I: 0         | NR                  | In situ: 0   | Positive: 87  |
|      |              | III: 88        |                     | Invasive: 88  | Positive: 87  |
|      |              | Missing: 0     |                     | Missing: 0   | Negative: 87  |
|      |              |                |                     |               | Missing: 0    |
| 2008 | Ueda45       | NR             | Tis: 7              | In situ: 7   | Positive: 106 |
|      |              |                | T1: 32              | Invasive: 67  | Negative: 106 |
|      |              |                | T2: 33              | Missing: 0   | Missing: 2    |
|      |              |                | T3: 2               |               |               |
|      |              |                | T4: 0               |               |               |
|      |              |                | Missing: 0          |               |               |
| 2019 | Valente46    | 0: 0           | Tis: 0              | In situ: 0   | Positive: 350 |
|      |              | I: 208         | T1: 272             | Invasive: 458 | Negative: 106 |
|      |              | II: 189        | T2: 151             | Missing: 0   | Missing: 2    |
|      |              | III: 61        | T3: 27              |               |               |
|      |              | Missing: 0     | T4: 8               |               |               |
| 2007 | Vaughan47    | 0: 40          | Tis/T1: 107         | In situ: NR  | Positive: 87  |
|      |              | I: 41          | T2: 80              | Negative: 87  |
|      |              | II: 65         | T3: 13              | Negative: 87  |
|      |              | III: 64        | T4: 10              | Negative: 87  |
|      |              | Missing: 0     | Missing: 0          | Negative: 87  |
| 2020 | Wu57         | 0: 199         | Tis: 199            | In situ: 199 | Positive: 173 |
|      |              | Missing: 0     | Missing: 0          | Negative: 173 |

(Continued)
TABLE 3. Continued

| Year | First author | AJCC stage (n) | T classification (n) | Histology (n) | ER (n) | PR (n) | Her2Neu (n) |
|------|--------------|---------------|---------------------|--------------|--------|--------|------------|
| 2020 | Wu           | NR            | Tis/T0: 44          | In situ: NR  | Positive: 101  | Positive: 26  | Positive: 114  |
|      |              |               | T1: 122             | Invasive: 316 | Positive: 153 | Positive: 21  | Positive: 209  |
|      |              |               | T2: 115             | Other: 7     | Missing: 0   | Negative: 89  | Negative: 89   |
|      |              |               | T3: 42              |             | Positive: 234 | Positive: 89  | Negative: 89   |
|      |              |               | T4: 0               |             | Missing: 0   | Negative: 89  | Negative: 89   |
|      |              |               | Missing: 0          |             |          | Missing: 0   | Missing: 0     |

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; ER, estrogen receptor; NR, not reported; PR, progesterone receptor.

Fourteen studies\textsuperscript{9,13,19,21,22,24,26,28,30,39,40,52,56,62} reported on regional recurrence (Fig. 2B, $I^2 = 40.1\%$ [95\% CI, 0.0\%–68.2\%]). Eleven studies\textsuperscript{9,13,19,21,22,24,26,28,30,40–42,52,58,63–65,67,68} ($I^2 = 0.19$) included 3454 patients with I-ABR, and three studies\textsuperscript{9,13,19} ($I^2 = 0$) included 674 patients with D-ABR (Table S3a). In the I-ABR group, 83 (2.4\%) regional recurrences occurred, and 14 (2.1\%) in the D-ABR group. Their weighted average proportions were 0.02 (95\% CI, 0.01–0.03) and 0.02 (95\% CI, 0.01–0.03), respectively.

Locoregional recurrence after autologous PMBR was reported by 16 studies\textsuperscript{8,13,21,22,28,30,40–42,52,58,63–65,67,68} (Fig. 2C, $I^2 = 72.2\%$ [95\% CI, 55.3\%–82.6\%]). Of those, 15 studies\textsuperscript{8,21,22,28,30,40–42,52,58,63–65,67,68} reported on I-ABR ($I^2 = 0.40$), and the weighted average proportion of locoregional recurrences was 0.04 (95\% CI, 0.03–0.06). In the three studies that reported on D-ABR\textsuperscript{8,13,65} ($I^2 = 0.86$), the weighted average proportion of locoregional recurrence was 0.01 (95\% CI, <0.01–0.03).

Twenty-five studies\textsuperscript{4,8,9,13,19,21,22,24–26,28–30,40–42,50,52,56,62–65,67,68} (Fig. 2D, $I^2 = 86.0\%$ [95\% CI, 80.9\%–89.8\%]) reported occurrence of distant metastasis after autologous PMBR, of which 22 studies\textsuperscript{4,8,21,22,24–26,28–30,40–42,50,52,56,62–65,67,68} ($I^2 = 0.85$) included 5476 patients with I-ABR, and 6 studies\textsuperscript{8,9,13,19,50,65} ($I^2 = 0.75$) included 1380 patients with D-ABR (Fig. 1D). In total, 368 of 5476 patients (6.7\%) developed distant metastasis after I-ABR, and 125 of 1380 patients (9.1\%) developed distant metastasis after D-ABR (Table S3a). The heterogeneity among these studies was too high to pool the results. Therefore, no weighted average proportion is reported.

Finally, 26 studies\textsuperscript{8,9,13,19,21,24,26,28–30,40–43,46,52,56,58,59,62–65,67,68} reported total breast cancer recurrence in autologous PMBR (Fig. 2E, $I^2 = 89.7\%$ [95\% CI, 86.6\%–92.5\%]). Twenty-two studies\textsuperscript{8,21,24,26,28–30,40–43,46,52,56,58,59,62–65,67,68} ($I^2 = 0.50$), representing 5723 patients after I-ABR, reported 578 recurrences (10.1\%, Table S3a). Six studies\textsuperscript{8,9,11,13,19,65} ($I^2 = 0.50$), including 1473 patients after D-ABR, reported 191 recurrences (13.0\%). Again, the high heterogeneity among these studies did not allow pooling of the data.

In conclusion, delayed autologous PMBR did not lead to different local, regional, and locoregional breast cancer recurrence rates than immediate autologous PMBR. Although it seems that there are no statistically significant differences in distant metastasis or overall breast cancer recurrence rates between immediate and delayed autologous PMBR, we could not calculate reliable weighted average proportions for these outcome measures due to a too high heterogeneity among the studies. Therefore, it was not possible to draw a solid conclusion on whether delayed autologous PMBR leads to higher distant metastasis and total breast cancer recurrence rates than immediate autologous PMBR.

**Immediate versus delayed implant-based PMBR**

In total, 22 studies\textsuperscript{31–38,42,47–49,54,55,57,59–61,64,66–68} reported local recurrence after immediate implant-based post-mastectomy breast reconstruction (I-IBR) (Fig. 3A, $I^2 = 42.1\%$ [95\% CI, 3.8\%–65.1\%]). These studies ($I^2 = 0.27$) included 4121 patients, of whom 146 (3.5\%) developed local recurrences (Table S3b). The weighted average proportion of local recurrences was 0.03 (95\% CI, 0.02–0.04).

Proportions of regional recurrences after I-IBR were reported in 10 studies\textsuperscript{31–33,35,38,45,55,57,59–61,64,66–68} ($I^2 = 61.2\%$ [95\% CI, 22.6\%–80.5\%]), including 79 regional recurrences in 2446 patients (3.2\%) (Fig. 3B; Table S3b). The weighted average proportion of local recurrences was 0.02 (95\% CI, 0.01–0.04).

Fifteen studies\textsuperscript{20,31–33,35,41,42,53,55,57,59–61,64,66–68} ($I^2 = 56.4\%$ [95\% CI, 22.4\%–75.5\%]) reported locoregional recurrences after implant-based PMBR (Fig. 3C).
| Year | First author | Mastectomy type | Chemotherapy | Radiotherapy | Hormone therapy |
|------|--------------|-----------------|--------------|--------------|-----------------|
| 2014 | Adam         | Skin- and nipple-sparing: 69 | Neo-adjuvant/adjuvant: Yes 6/19 | Yes: 22 | Yes: 41 |
|      |              | Missing: 0      | No/missing: NR/NR | No/missing: NR  | No/missing: NR  |
| 2018 | Adam         | NR              | Neo-adjuvant/adjuvant: Yes: 94/157 | Yes: 209 | Yes: 191 |
|      |              |                | No: 160/96 | No: 44 | No: 63 |
|      |              |                | Missing: 1/1 | Missing: 1 | Missing: 1 |
| 2019 | Bjöhle       | NR              | Neo-adjuvant/adjuvant: Yes: 31/79 | Yes: 128 | Yes: 95 |
|      |              |                | No: 97/48 | No: 0 | No: 32 |
|      |              |                | Missing: 0/1 | Missing: 0 | Missing: 1 |
| 2006 | Caruso       | Skin- and nipple-sparing: 51 | Yes: 12 | Yes: 3 | Yes: 21 |
|      |              | Missing: 0      | No: 39 | No: 48 | No: 30 |
|      |              |                | Missing: 0 | Missing: 0 | Missing: 0 |
| 2018 | Chen         | NR              | Yes: 110 | Yes: 111 | Yes: 77 |
|      |              |                | No: NR | No: NR | No: NR |
|      |              |                | Missing: 0 | Missing: 0 | Missing: 0 |
| 2017 | Cont         | Skin- and nipple-sparing: 518 | Yes: 253 | Yes: 94 | Yes: 420 |
|      |              | Missing: 0      | No/missing: NR | No/missing: NR | No/missing: NR |
| 2016 | Dillekás     | NR              | Yes: 143 | Yes: 191 | Yes: 136 |
|      |              |                | No: 144 | No: 117 | No: 117 |
|      |              |                | Missing: 25 | Missing: 59 | Missing: 59 |
| 2017 | Du           | Skin- and nipple-sparing: 157 | NR | Yes: 18 | NR |
|      |              | Missing: 0      | No/missing: NR | NR | NR |
| 2020 | Early        | Conventional mastectomy, skin-sparing mastectomy, and nipple-areola skin-sparing mastectomy: NR | NR | NR | NR |
| 2011 | Eriksen      | NR              | Neo-adjuvant/adjuvant: Yes: 39/132 | Yes: 99 | Yes: 209 |
|      |              |                | No: NR/NR | No: NR | No: NR |
|      |              |                | Missing: 0/8 | Missing: 11 | Missing: 17 |
| 2016 | Fujimoto     | Skin- and nipple-sparing: 136 | Neo-adjuvant: Yes: 25 | NR | NR |
|      |              | Skin-sparing: 36 | No/missing: NR | NR | NR |
|      |              | Missing: 0      | Missing: 0 | Missing: 0 | Missing: 0 |
| 2018 | Geers        | NR              | NR | NR | NR |
| 2005 | Greenway     | Skin-sparing: 225 | NR | NR | NR |
| 2020 | Ha           | Implant-based/autologous: Skin- and nipple-sparing: 68/58 | Implant-based/autologous: Yes: 136/132 | Yes: 51/48 | Yes: 51 |
|      |              | Skin-sparing: 64/84 | No: 111/117 | No: 195/200 | No: 195/200 |
|      |              | Total/conventional mastectomy: 115/107 | Missing: 0/0 | Missing: 1/1 | Missing: 1/1 |
| 2008 | Hölmich      | NR              | Yes: 165 | Yes: 116 | Yes: 24 |
|      |              |                | No/M: NR | No: 464 | No: NR |
|      |              |                | Missing: NR | Missing: 0 | Missing: NR |
| 2006 | Huang        | Modified radical mastectomy: 82 | Yes: 82 | Yes: 82 | “All patients with ER- or PR-positive receptor” |
|      |              | Missing: 0      | No: 0 | No: 0 | |
|      |              |                | Missing: 0 | Missing: 0 | |
| 2011 | Isern        | NR              | Yes: 48 | Yes: 109 | Yes: 33 |
|      |              |                | No: 77 | No: 16 | No: 92 |
|      |              |                | Missing: 0 | Missing: 0 | |
| 2010 | Kim          | Skin- and nipple-sparing: 152 | NR | Yes: 38 | NR |
|      |              | Skin-sparing: 368 | No/missing: NR | No/missing: NR | |
| 2017 | Kim          | Skin-sparing: 65 | Yes: 29 | Yes: 1 | Yes: 50 |
|      |              | Missing: 0      | No: 36 | No: 64 | No: 15 |
|      |              |                | Missing: 0 | Missing: 0 | Missing: 0 |
| 2016 | Lee          | Modified radical mastectomy: 213 | Yes: 213 | Yes: 213 | “All hormonal receptor-positive patients” |
|      |              | Missing: 0      | No: 0 | No: 0 | |
|      |              |                | Missing: 0 | Missing: 0 | |
| 2020 | Lee          | Skin- and nipple-sparing: 111 | Neo-adjuvant/adjuvant: Yes: 29/182 | Yes: 52 | NR |
|      |              | Skin-sparing: 327 | No: NR Missing: NR | No/missing: NR | |

(Continued)
### TABLE 4. Continued

| Year | First author | Mastectomy type | Chemotherapya | Radiotherapya | Hormone therapyb |
|------|--------------|-----------------|---------------|---------------|-----------------|
| 2018 | Lee26        | Skin- and nipple-sparing: 1032 | Yes: 603 | Yes: 87 | Yes: 648 |
|      |              | Missing: 0 | No: 423 | No: 940 | No: 377 |
|      |              |               | Missing: 6 | Missing: 5 | Missing: 7 |
| 2019 | Lee27        | Skin-sparing: 118 | Yes: 93 | Yes: 17 | Yes: 80 |
|      |              | Missing: 0 | No: 26 | No: 102 | No: 39 |
|      |              |               | Missing: 0 | Missing: 0 | Missing: 0 |
| 2012 | Lee24        | Skin- and nipple-sparing: 361 | NR | NR | NR |
|      |              | Skin-sparing: 510 | NR | NR | NR |
|      |              | Modified radical mastectomy: 29 | Missing: 100 | Missing: 6 | Missing: 7 |
| 2013 | Liang28      | Skin-sparing: 249 | Yes: 16/196 | Yes: 32 | Yes: 126 |
|      |              | Missing: 0 | No: NR/NR | No: NR/NR | No: NR/NR |
| 2013 | Lindford13   | Nonskin-sparing: 112 | Yes: 91 | Yes: 76 | Yes: 83 |
|      |              | Missing: 0 | No: 21 | No: 36 | No: 29 |
| 2010 | Lim63        | Skin- and nipple-sparing: 14 | Yes: 86 | Yes: 49 | Yes: 65 |
|      |              | Skin-sparing: 73 | No: 1 | No: 38 | No: 22 |
|      |              | Missing: 0 | Missing: 0 | Missing: 0 | Missing: 0 |
| 2017 | Maalouf50    | Skin-sparing: 40 | Immediate/delayed: 24/22 | Immediate/delayed: 30/32 | Immediate/delayed: 17/23 |
|      |              | Modified radical mastectomy: 22 | Missing: 0 | Missing: 0 | Missing: 0 |
|      |              | Missing: 0 | No/missing: NR/NR | No/missing: NR/NR | No/missing: NR/NR |
| 2008 | McCarthy53   | NR | Yes: 238 | Yes: 67 | NR |
|      |              | Missing: 2 | No: 69 | No: 236 | NR |
|      |              |                  | Missing: 0 | Missing: 303 | |
| 2020 | Metere60     | Skin- and nipple-sparing: 894 | Yes: 215/264 | Yes: 87 | NR |
|      |              | Missing: 0 | No/missing: NR/NR | No/missing: NR | |
| 2010 | Min6         | NR | Yes: 72 | Yes: 48 | NR |
|      |              | Missing: 0 | No: 111 | Missing: 0 | |
| 2013 | Munhoz54     | Skin- and nipple-sparing: 106 | Yes: 28 | Yes: 10 | NR |
|      |              | Missing: 0 | No/missing: NR | No/missing: NR | |
| 2017 | Murphy55     | Skin- and nipple-sparing: 240 | NR | NR | NR |
|      |              | Missing: 0 | No/missing: NR | NR | |
| 2005 | Mustonen56   | Skin- and nipple-sparing: 21 | NR | NR | NR |
|      |              | Subcutaneous: 34 | No/missing: NR | NR | |
|      |              | Nonskin-sparing: 1 | No/missing: NR | NR | |
| 2015 | Narui29      | Skin- and nipple-sparing: 152 | Yes: 43 | Yes: 15 | Yes: 120 |
|      |              | Skin-sparing: 53 | No/missing: NR | No/missing: NR | No/missing: NR |
|      |              | Missing: 0 | No/missing: NR | No/missing: NR | No/missing: NR |
| 2012 | Nava36       | Skin- and nipple-sparing: 59 | Yes: 26 | Yes: 10 | Yes: 38 |
|      |              | Missing: 0 | No/missing: NR | No/missing: NR | No/missing: NR |
| 2014 | Ota36        | Skin- and nipple-sparing: 2 | Yes: 60 | Yes: 2 | Yes: 91 |
|      |              | Skin-sparing: 131 | No: 73 | No/missing: NR | No: 42 |
|      |              | Missing: 0 | Missing: 0 | No/missing: NR | Missing: 0 |
| 2020 | Ozmen61      | Skin- and nipple-sparing: 75 | NR | Yes: 23 | NR |
|      |              | Missing: 0 | No/missing: NR | |
| 2016 | Park40       | Skin- and nipple-sparing: 36 | Yes: 136 | Yes: 19 | NR |
|      |              | Skin-sparing: 78 | No: 53 | No: 170 | |
|      |              | Missing: 0 | Missing: 0 | Missing: 0 | |
| 2020 | Parvez66     | Skin- and nipple-sparing: 175 | Yes: 49 | Yes: 40 | NR |
|      |              | Missing: 0 | No/missing: NR | No/missing: NR | |
| 2012 | Patterson30   | Skin-sparing: 170 | Yes: 105 | Yes: 51 | Yes: 65 |
|      |              | Modified radical mastectomy: 142 | No/missing: NR | No/missing: NR | No/missing: NR |
| 2011 | Reddy41      | NR | Yes: 181 | Yes: 135 | Yes: 232 |
|      |              | Missing: 0 | No: 313 | No: 359 | No: 262 |
| 2012 | Romics42     | Skin-sparing: 207 | Yes: 100 | Yes: 72 | Yes: 126 |
|      |              | Missing: 0 | No: 107 | No: 81 | No: 27 |
|      |              |                  | Missing: 0 | Missing: 54 | Missing: 54 |
Fourteen studies\textsuperscript{31–33,35,41,42,53,55,57,58,60,64,67,68} included 2793 patients in the I-IBR group, of whom 139 patients (5.0\%) developed locoregional recurrences (Table S3b). Their weighted average proportion was 0.03 (95\% CI, 0.01–0.05). One study\textsuperscript{20} reported 49 locoregional recurrences in 580 patients (8.4\%) after delayed implant-based post-mastectomy breast reconstruction (D-IBR), representing a proportion of 0.08 (95\% CI, 0.06–0.11).

Eighteen studies\textsuperscript{20,31,33–36,38,41,42,48,54,55,57,60,64,66,67,69} (Fig. 3D, \(I^2 = 88.6\%\) [95\% CI, 83.5\%–92.1\%]) described the occurrence of distant metastasis after implant-based PMBR, of which 17\textsuperscript{31,33–36,38,41,42,48,54,55,57,60,64,66,67,69} reported distant metastases after I-IBR (\(T^2 = 0.55\)); in total, 177 of 3022 patients (5.9\%) developed distant metastases after I-IBR (Table S3b). However, the high heterogeneity among these studies did not allow pooling of the data. One study\textsuperscript{20} reported 86 distant metastases in 580 patients (14.8\%) after D-IBR, representing a proportion of 0.15 (95\% CI, 0.12–0.18).

Twenty studies\textsuperscript{20,31,33–36,38,41–43,46,48,53,57–59,60,64,66–68} (\(I^2 = 89.2\%\) [95\% CI, 84.7\%–92.3\%]) reported overall recurrences after implant-based PMBR, of which 19 studies\textsuperscript{48,50–53,55,58–60,63,65,70,74–76,89,98,100,109} (\(T^2 = 0.32\)) reported data on 353 recurrences (11.7\%) (Table S3b). High heterogeneity did not allow pooling of the data. One study\textsuperscript{20} reported 145 (25.0\%) overall recurrences among 580 patients after D-IBR (0.25 [95\% CI, 0.22–0.29]).

In summary, the data were too heterogeneous to calculate weighted average proportions for distant and total breast cancer recurrences after I-IBR. Moreover, none of the studies reported local or regional recurrence rates after D-IBR, and only one study\textsuperscript{20} reported locoregional recurrence, distant metastasis, and total recurrence rates after D-IBR (Table S3b). Consequently, there were insufficient data to calculate weighted average proportions of local, regional, locoregional, distant, or total breast cancer recurrence rates after D-IBR. Therefore, it was not possible to compare local, regional, locoregional, distant, or total recurrence rates between I-IBR and D-IBR.

DISCUSSION

This SR/MA, including studies of moderate-level quality, showed that delayed autologous PMBR does not lead to different local, regional, and locoregional breast cancer recurrence rates compared to immediate autologous PMBR. Data of the included studies were either insufficient or too heterogeneous to evaluate whether delayed autologous...
PMBR leads to different distant metastasis or overall breast cancer recurrence rates compared to immediate autologous PMBR, or whether delayed implant-based PMBR led to higher breast cancer recurrence and distant metastasis rates than immediate implant-based PMBR. This meta-analysis is the first to focus on the differences in oncological outcomes after immediate versus delayed PMBR for autologous and implant-based PMBR separately.

Consistent with our results, Shen and colleagues (2020) observed no difference in recurrence rates after immediate and delayed PMBR in their systematic review. Similarly, in a meta-analysis by Gieni and colleagues (2012), no difference was found in local recurrences between immediate PMBR and mastectomy only. However, both reviews were limited by the absence of stratified data on type of reconstruction (i.e., autologous and/or implant-based). Similar limitations were present in a review by Tsoi and colleagues, comparing implant-based with autologous PMBR while not considering the timing of reconstruction. Both distinctions are important for clinical decision-making, because surgical impact and postoperative complications differ greatly between implant-based and autologous breast reconstructive surgery and between immediate and delayed breast reconstructions. Ha and colleagues were the first to compare oncological safety between immediate reconstructive methods. To provide robust evidence that supports clinical and shared decision-making, prospective studies focusing on both surgical methods and both timings of reconstructive surgery separately are needed.

Personalized health care is increasingly becoming standard of care for patients with breast cancer. Ideally, each patient’s treatment strategy is aligned with patients’ genotypic, phenotypic and clinical characteristics, as well as patients’ personal preferences. Subsequently, decision aids (DAs) to support shared decision-making (SDM) are gaining popularity. However, breast reconstruction DAs are predominantly designed for general patient education about different reconstructive options and at best predict the risk of postoperative complications. Because of lack of detailed data on oncological outcomes after different methods and timings, it is not surprising that information on oncological outcomes is not included in current DAs. Moreover, due to various reasons (e.g., previous surgery or radiotherapy, body type), not all patients are eligible for all reconstructive options. To support SDM and improve personalized patient information, patient education should be adjusted to the specific characteristics of the individual. This tailored information can only be achieved through better understanding of differences in oncological outcomes after PMBR.

Another important aspect of clinical decision-making in the field of breast reconstructive surgery concerns the potential influence of specific reconstructive types and timings on the overall breast cancer treatment strategy. Immediate PMBR does not delay time to adjuvant chemotherapy to a clinically relevant extent. However, the timing of PMBR when radiotherapy is indicated, is still controversial. To enhance personalized medicine, better understanding of oncological risks within subgroups will allow more profound assessments of individual risks in a multidisciplinary setting, thereby improving quality of care.

Better insight in recurrence rates and recurrence patterns after different reconstructive techniques may also improve postoperative surveillance strategies. To date, no consensus exists on routine imaging of the reconstructed breast. Physical examination is mostly used to detect locoregional recurrences after PMBR, but deeper located recurrences (i.e., chest wall recurrences) may be missed. Although Shammas and colleagues did not find a difference in disease-free survival between reconstructed patients who received postoperative imaging for surveillance versus those who did not, routine imaging may still be of added clinical value after specific reconstructive techniques or in patients with certain risk profiles. In example, due to preservation of the skin envelope, immediate autologous PMBR might form a risk for developing local recurrences. Because approximately two thirds of all patients with locoregional recurrences will develop distant metastasis, larger studies are needed to define the role of routine mammography, ultrasound, and/or magnetic resonance imaging for early detection of locoregional recurrences.

Most importantly, the low risk of locoregional breast cancer recurrence and distant metastasis after breast cancer treatment makes it hard to generate robust evidence-based conclusions about oncological outcomes after the various reconstructive timings and techniques, and recommendations for breast cancer surveillance after PMBR. As a result, patient education on which type and timing of breast reconstruction patients qualify for remains highly sensitive to experts’ beliefs (e.g., the tumor dormancy theory), preferences, resources, and experience. As such, breast reconstructive options that are offered vary widely, even on regional levels.

In addition to the generally low recurrence rates after breast cancer treatment, other challenges of many studies on PMBR are the heterogeneity in study populations and follow-up, and their susceptibility for confounding by indication. This was illustrated by the large variation
in recurrence rates found in our analyses. For example, recurrence rates for distant metastasis and overall breast cancer recurrences after D-1BR, as reported by Hölmich and colleagues, seem high in comparison to other subgroups. However, their high recurrence rates could be explained by the fact that only patients with invasive breast carcinoma were included, that patients were treated between 1978 and 1992, and by their long follow-up of 10 years. Although we recognize the challenges researchers are faced with when performing studies concerning PMBR, we would like to emphasize the need for larger, prospective long-term follow-up studies focusing on PMBR and oncological outcomes in order to increase equal education on, and access to various reconstructive options. The use of prospectively maintained databases and intensive collaboration between existing registries such as oncological, pathological, and surgical registries (e.g., the Dutch Breast Implant Registry or the UK Flap registry) will help overcome these challenges. Transparent, uniform, and complete data collection can be improved by implementation of standardized reporting formats in electronic medical patient records.

This meta-analysis has several limitations inherent to the quality of the included studies. Despite efforts to minimize heterogeneity among the study populations by only including studies reporting outcomes per subgroup (i.e., autologous delayed and immediate, implant-based delayed and immediate) and applying strict in- and exclusion criteria, substantial heterogeneity was observed. Moreover, the definitions of local, regional, locoregional, and total recurrences were not always specified among studies and often one of these outcomes was not reported. However, we did not exclude studies lacking a detailed description of their outcome measure to ensure we could use all data of all available studies, given that they complied with our predefined level of quality, to support a data-driven conclusion. Because of the nonrandomized nature of the studies and lack of high-quality trials, the risk of selection bias and confounding in the included studies is substantial. However, performing randomized trials for breast reconstructive surgery and oncological safety is often considered unethical or unfeasible. By requesting specified data of subgroups from authors who only reported outcomes for the entire groups, selection bias due to unavailability of studies was reduced. Subgroup or adjusted analyses based on tumor stage were not feasible due to incomplete and/or unstratified data. Last, considering that multiple different groups were compared, although formal testing was not performed, there could be an issue with multiple testing. However, the included data allowed for only few formal comparisons. Therefore, we believe this potential issue is minor. We believe this would not have affected the interpretation of the results. A strength of these aggregated patient data (APD) meta-analyses is that it overcomes potential bias of narrative literature reviews, whereas summarizing data of many studies that were each too small to provide valid evidence. Furthermore, generalizability was strengthened by the large number of studies including a wide range of patient demographics and origins (i.e., Asia, Europe, North and South America).

In conclusion, delayed autologous PMBR leads to similar (loco)regional breast cancer recurrence rates as compared to immediate autologous PMBR. Data of the included studies were unfit to reliably conclude whether delayed autologous PMBR leads to different distant metastasis or overall breast cancer recurrence rates compared to immediate autologous PMBR, or whether delayed implant-based PMBR leads to different breast cancer recurrence and distant metastasis rates than immediate implant-based PMBR. Based on current evidence, oncological concerns do not seem a valid reason to withhold patients from certain reconstructive timings or techniques, and patients should equally be offered all reconstructive options they technically qualify for.

However, these results are based on moderate-level quality studies and therefore do not allow firm conclusions regarding oncological outcomes after different types and timings of PMBR. As such, it remains challenging to define evidence-based recommendations. In support of equal access to care and better patient selection for breast reconstructions, prospective and sufficiently powered studies evaluating long-term oncological outcomes are needed to confirm oncological safety after different breast reconstructive timings and techniques in the treatment of patients with breast cancer.

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AUTHOR CONTRIBUTIONS

Claudia A. Bargon: Conception or design of the work, acquisition of data for the work, analysis of data for the work, interpretation of data for the work, drafting the work, critical revision of the work for important intellectual content, and responsibility for overall content as a guarantor. Danny A. Young-Afat: Conception or design of the work, analysis of data for the work, drafting the work, and critical revision of the work for important intellectual content. Mehmet Ikinci: Acquisition of data for the work, analysis of data for the work, interpretation of data for the work, and critical revision of the work for important intellectual content. Assa Braakenburg: Conception or design of the work, interpretation of data for the work, and critical revision of the
work for important intellectual content. Hinne A. Rakhorst: Conception or design of the work, interpretation of data for the work, and critical revision of the work for important intellectual content. Marc A.M. Mureau: Conception or design of the work, acquisition of data for the work, drafting the work, and critical revision of the work for important intellectual content. Ahlen M. Verkooijen: Conception or design of the work, acquisition of data for the work, and critical revision of the work for important intellectual content. Annemiek Doeke: Conception or design of the work, acquisition of data for the work, analysis of data for the work, interpretation of data for the work, drafting the work, critical revision of the work for important intellectual content, and responsibility for overall content as a guarantor. All authors have given final approval for the version of this article to be published and have agreed to be accountable for all aspects of the work and thereby ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST
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