Abdominoperineal Resection Provides Better Local Control But Equivalent Overall Survival to Local Excision of Anorectal Malignant Melanoma

A Systematic Review

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Objective: To determine whether the extent of surgery is associated with survival in anorectal malignant melanoma (ARMM).

Background: ARMM is a rare and highly malignant neoplasm with unfavorable prognosis. The optimal surgical management, abdominoperineal resection (APR) or local excision (LE), has been long debated, but conclusive evidence has not been obtained.

Methods: A comprehensive electronic literature search was performed to identify studies evaluating survival between APR and LE for ARMM. The main outcome measures were overall survival, relapse-free survival, and local recurrence. A meta-analysis was performed using the random-effects models to calculate the odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Thirty-one studies, with a total of 1006 patients [544 (54.1%) APR and 462 (45.9%) LE], were included. Meta-analyses showed that overall survival (OR, 1.14; 95% CI, 0.74–1.76; P = 0.54) and relapse-free survival (OR, 0.95; 95% CI, 0.43–2.09; P = 0.89) did not differ significantly between the APR and LE groups. APR significantly reduced local recurrence compared with LE (OR, 0.18; 95% CI, 0.09–0.36; P = 0.00001).

Conclusions: Although several limitations, such as inclusion of only retrospective studies with relatively small sample size and selection biases for surgical procedure, are involved, this meta-analysis suggested that APR has no survival benefit; however, APR confers better local control than LE. Given that local failures after LE could be managed by salvage surgery, minimizing morbidity and maximizing quality of life should be the focus in surgical treatment of ARMM.

Keywords: anorectum, local recurrence, malignant melanoma, surgery, survival

(Ann Surg 2014;00:1–8)

Anorectal malignant melanoma (ARMM) is a rare neoplasm that was first reported by Moore in 1857.1 It accounts for less than 1% of all malignant melanomas and less than 4% of anal canal malignancies. The anorectum is the most frequent site for malignant melanoma in the gastrointestinal tract.2,3 Approximately 20% of these lesions are amelanotic microscopically, and patients present with nonspecific symptoms such as anal discomfort or hematochezia, making the diagnosis difficult.1 Delayed therapeutic intervention after initial diagnosis and highly malignant potential contribute to poor outcome of ARMM. Unfortunately, the tumor is usually widely metastasized by the time that a definitive diagnosis is reached. This, coupled with poor response to radio- and chemotherapy, narrows down the treatment options. The majority of patients die of distant metastasis, and reported overall 5-year survival is less than 20%.3,4 Surgical management is still the mainstay of treatment for ARMM.

There has been a long debate regarding the optimal surgical treatment—whether abdominoperineal resection (APR) or local excision (LE)—in terms of oncological outcomes and quality of life. Historically, APR was common and considered as a reasonable procedure in expectation of extensive disease control in early studies limited to small case series.6–8 However, subsequent relatively large case review series have reported similar oncological outcomes for LE compared with APR and superior quality of life after surgery.1,3–13

Owing to its low incidence, designing a prospective study is unrealistic, and only retrospective, relatively small sample reviews are available to date. This has hampered collection of conclusive evidence when considered independently regarding the optimal surgical approach for ARMM. We, therefore, conducted a meta-analysis to conclude the long-debated comparison of long-term outcomes between APR and LE for ARMM, including overall survival (OS), relapse-free survival (RFS), and local recurrence, with a sufficiently large sample size (n = 1006).

METHODS

This meta-analysis was performed in accordance with the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009.14

Search Methods for Identification of Studies

We performed a systematic literature review in MEDLINE (searched through PubMed), Google Scholar, and the Cochrane Database to identify all studies published up to August 2013, comparing predefined outcomes in subjects who underwent APR or LE for ARMM. The search was performed using the terms “anorectal malignant melanoma,” “surgery,” “abdominoperineal resection,” “local excision,” “recurrence,” and “survival” as key words. In addition, the related article function was used to broaden the search, and all abstracts, studies, and citations retrieved were scanned for subject relevance. Complete articles of all potentially relevant publications were retrieved and formally evaluated for inclusion. References of all relevant publications were hand-searched for additional studies overlooked using this search strategy, and this method of cross-referencing was continued until no further relevant publications were identified.

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Disclosure: The authors did not receive any grant support. The authors declare no conflicts of interest.

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ISSN: 0003-4922/14/00000-0001
DOI: 10.1097/SLA.0000000000000862
Data Extraction

Extracted data included the primary author’s name, year of publication, country and institutions in which the study was performed, journal, study design, period of subject enrollment, number of included subjects and their characteristics (including age, sex, and tumor-related variables such as size and thickness), and surgery-related variables (type of surgery, curability, mortality, adjuvant therapy, follow-up period, and all available long-term outcomes). Each retrieved publication was evaluated independently by 2 investigators (A. M. and T. K.) for inclusion or exclusion.

Inclusion and Exclusion Criteria

We defined inclusion and exclusion criteria a priori. All original publications reporting absolute numbers of 1 or more of the predefined outcomes of interest, including OS, RFS, and local recurrence, in subjects with ARMM who underwent APR or LE were eligible, irrespective of study design. Articles written in English were eligible. Studies that failed to fulfill the inclusion criteria were excluded. Extracted data were cross-checked to reach consensus and entered into a computerized spreadsheet for analysis.

Statistical Analysis

Dichotomous variables were analyzed by assessing the odds ratio (OR), which represented the odds of an adverse event occurring in the APR compared with the LE group, along with 95% confidence interval (CI). An OR of less than 1 favored the APR group, and the point estimate of the OR was considered statistically significant at the P < 0.05 level if the 95% CI did not include the value 1. We used the Mantel-Haenszel method to combine the OR for the outcomes of interest. A random-effects meta-analytical technique was applied, in which it was assumed that there were variations between studies, making the calculated OR more conservative than with a fixed effects model. Patients who underwent surgery at different centers may have had different risk profiles and selection criteria for each surgical technique; therefore, the random-effects model was utilized to take this heterogeneity into account. Meta-analysis was performed using RevMan for Windows version 5 (Cochrane Collaboration, Software Update, Oxford, London, United Kingdom). In the tabulation of the results, squares indicate the point estimates of the treatment effects (OR), with 95% CIs indicated by the horizontal bars. The diamond represents the summary estimate from the pooled studies with 95% CIs. Cochran χ²-based Q test was applied to assess between-study heterogeneity. F test was used to test the heterogeneity between the included studies. Publication bias was assessed by visual examination of a funnel plot, with asymmetry formally assessed with Egger’s linear regression test15 and the rank correlation test (Begg test) using “WINPEPI” software (http://www.brixtonhealth.com/pepi4windows.html).16

RESULTS

Literature Search and Selected Studies

Details of the literature search are shown in Figure 1. From 303 citations retrieved through the database search, 51 potential articles were identified. The other 252 were excluded based on title and abstract review. Twelve were added by the related article function or manual search. Of 63 full-text articles evaluated, 32 were excluded by full-text article review. Of these, 3 comparative studies and 10 non-comparative studies were included in the final analysis. The 31 remaining studies,6–13,17–39 published between 1966 and 2013, which compared the predefined outcomes of interest, including OS, and/or RFS, and/or local recurrence, between APR and LE groups for ARMM, matched our inclusion criteria and were deemed suitable for this meta-analysis. Detailed characteristics of the included studies are shown in Table 1. Of 1006 patients included in these 31 studies,6–13,17–39 544 (54.1%) underwent APR and 462 (45.9%) underwent LE for ARMM as initial surgical treatment. The design of all 31 studies was retrospective review.6–13,17–39 Fourteen studies6–8,10,13,18,20,24,26,28,29,31,32,34 originated from the United States,10,11,12,17,19,23,23,30,33,37 from Europe,6,21,22,25,35,38,39 from Asia, and 1 from South America. Five studies utilized nationwide database as a source of data.12,23,24,26,30 The number of patients in each study ranged from 5 to 152. Fifty to 60 years was a common onset age of ARMM, and women were more likely than men to be diagnosed. Twenty-six studies6–10,12,13,18,20,23,24,26,27,32–37,39 clearly mentioned that only subjects who underwent curative resection were included in each study. The application of adjuvant therapy such as chemotherapy, radiation, and immunotherapy was mentioned in 16 studies6,9,11,12,17–24,26,28,31,33,34,37,38. Regarding long-term outcomes in each group, 31 studies6–13,17–39 evaluated OS. Fourteen studies6,9,10,13,17,19,20,22,24,31–36,38 reported RFS, and local recurrence was evaluated in 13 studies.6,9,11,12,18,20,21,26,27,32,34,38,39 If the study provided only a survival curve, and not the survival rate, we obtained the rate by extracting data as accurately as possible from the figure and calculating the number of events. In the conclusion of each study, APR was recommended for ARMM in 7 studies.6–8,22,25,27 In contrast, 11 studies recommended LE.6,9,11,13,18,20,28,32,33,36,39 The remaining 13 studies reported no superiority of either procedure.10,17,19,21,23,24,29–31,34,35,37,38

Long-term Outcomes

Data on 5-year OS were available in 30 studies6–13,17–27,29–39 with the overall rate being 19.2%. Five-year OS rates in the APR and LE groups of these 30 studies6–13,17–29,39 were 18.7% and 19.9%, respectively. The study of Malik et al28 reported that 2-year OS data and the rates in the APR and LE groups were 43.0% and 70.0%, respectively. This relatively short-term outcome of Malik et al28 was integrated into the data from 30 other studies6–13,17–29,39 for final meta-analysis to increase sample size, which evaluated a total of 1006 patients. No between-study heterogeneity was observed (P = 0.17; I² = 21%). Meta-analysis of the 31 studies6–13,17–39 showed that OS did not differ significantly between the APR and LE groups, with an OR of 1.14 (95% CI = 0.74–1.76; P < 0.05) (Fig. 2A). Visual inspection of the funnel plot for OS did not suggest the presence of publication bias (Fig. 2B), and no significant publication bias was observed on either the Egger (P = 0.677) or rank correlation (P = 0.444) tests.
## TABLE 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Reference, yr</th>
<th>Country</th>
<th>Design (Period)</th>
<th>Mean Age, yr</th>
<th>Male Sex (%)</th>
<th>Tumor Size, mm</th>
<th>Tumor Depth, mm</th>
<th>Cases APR</th>
<th>Cases LE</th>
<th>Only R0 Included</th>
<th>Adjuvant Therapy</th>
<th>Endpoints</th>
<th>Follow-up Period, mo</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al. (2011)</td>
<td>Korea</td>
<td>RS (1999–2008)</td>
<td>61</td>
<td>42.1</td>
<td>34</td>
<td>12</td>
<td>7</td>
<td>NS</td>
<td>Yes</td>
<td>Yes</td>
<td>OS, RFS,</td>
<td>4</td>
<td>APR</td>
</tr>
<tr>
<td>Thibault et al (1997)</td>
<td>United States</td>
<td>RS (1939–1993)</td>
<td>63</td>
<td>69.7</td>
<td>26</td>
<td>11</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NS</td>
<td>OS, RFS</td>
<td>66 mo to 44 yr</td>
<td>LE</td>
</tr>
<tr>
<td>Luna-Perez et al (1996)</td>
<td>Mexico</td>
<td>RS (NS)</td>
<td>66</td>
<td>46.2</td>
<td>47</td>
<td>6.4</td>
<td>6</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>OS, LR</td>
<td>11</td>
<td>APR</td>
</tr>
<tr>
<td>Siegal et al (1983)</td>
<td>Israel</td>
<td>RS (1960–1981)</td>
<td>64</td>
<td>43.3</td>
<td>15</td>
<td>9</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>OS, RFS</td>
<td>NS</td>
<td>LE</td>
</tr>
</tbody>
</table>

(Continues)
Thirteen studies\(^8,10,13,17,19,20,22,31–36\) evaluated 5-year RFS, with the overall rate being 17.2%. Five-year RFS rates in the APR and LE groups of these 13 studies\(^8,10,13,17,19,20,22,31–36\) were 16.9% and 17.7%, respectively. The study of Yen et al\(^18\) reported 2-year RFS data, and the rates in the APR and LE groups were 10.0% and 14.3%, respectively. This relatively short-term outcome of Yen et al\(^18\) was integrated into the data from 13 other studies\(^8,10,13,17,19,20,22,31–36\) for final meta-analysis to increase sample size, which evaluated a total of 328 patients. No between-study heterogeneity was observed \((P = 0.34; I^2 = 12\%)\). Meta-analysis of the 14 studies\(^8,10,13,17,19,20,22,31–36,38\) showed that RFS did not differ significantly between the APR and LE groups, with an OR of 0.95 \((95\% CI = 0.43–2.09; P = 0.89)\) (Fig. 3). No significant publication bias was observed on either the Egger \((P = 0.591)\) or rank correlation \((P = 0.352)\) tests.

Thirteen studies\(^5,9,11,12,18,20,21,26,27,32,34,38,39\) included in this meta-analysis investigated the effects of each procedure on local recurrence. The overall local recurrence rate was 37.7%: 21.6% in the APR group and 57.7% in the LE group. Heterogeneity among studies was not observed \((P = 0.19; I^2 = 25\%)\). Meta-analysis of the 13 studies\(^6,9,11,12,18,20,21,26,27,32,34,38,39\) showed that APR significantly reduced local recurrence in comparison with LE, with an OR of 0.18 \((95\% CI = 0.09–0.36; P < 0.00001)\) (Fig. 4). No significant publication bias was observed in either the Egger \((P = 0.547)\) or rank correlation \((P = 0.393)\) tests.

**Subgroup Analysis**

We extracted 4 factors that might have influenced long-term outcomes: sample size, era of publication, surgical curability, and country in which the study was conducted. Table 2 summarizes the results of the meta-analyses for 5-year OS, 5-year RFS, and local recurrence when considering studies in respective subgroups. When studies with 30 or more cases, published after 2000, only R0 resection, and originated from the United States, were assessed, no significant differences were observed between the APR and LE groups in terms of 5-year OS and RFS without significant between-study heterogeneity. In contrast, meta-analysis of studies with 30 or more cases, published after 2000, and only R0 resection showed significant reductions in local recurrence in the APR group compared with the LE group without significant between-study heterogeneity. However, the difference in the analysis of studies originated from the United States did not reach statistical significance.

**DISCUSSION**

This is believed to be the first meta-analysis comparing the long-term outcomes between APR and LE for ARMM, which included 31 studies with a total of 1006 patients. The analysis showed no significant differences between APR and LE in terms of OS and RFS. However, APR reduced local recurrence significantly compared with LE.

Both the total 5-year OS and 5-year RFS rates were relatively low (OS, 19.2%; RFS, 17.2%), which reflects the aggressive malignant potential of ARMM. Delay in instituting treatment because of difficulty in making a diagnosis and aggressive biology combine to make it an incurable disease. Up to 40% of patients may have distant metastases at the time of initial diagnosis.\(^10,13,40\) Although a study with 23 ARMM patients from MD Anderson Cancer Center reported that adjuvant radiotherapy after LE offers good local control (5-year local control rate, 74%),\(^41\) the impact of nonsurgical therapy including chemotherapy, immunotherapy, radiotherapy, and their combinations remains unclear.\(^42,43\) Surgical intervention is still the mainstay for ARMM; however, the optimal surgical procedure, APR or LE, has long been debated. In contrast to early studies of small case series reporting APR as the standard procedure for ARMM,
FIGURE 2. (A) Meta-analysis for OS between APR and LE for ARMM. (B) Funnel plot depicting the distribution of OR for the studies in this meta-analysis.
FIGURE 3. Meta-analysis for RFS between APR and LE for ARMM.

FIGURE 4. Meta-analysis for local recurrence between APR and LE for ARMM.

subsequent studies of relatively large case series reported that (1) APR has no survival benefit compared with LE; (2) LE has a higher local recurrence rate but recurrence frequently occurs concomitantly with distant metastasis, and local recurrence can be managed with salvage surgery; and (3) LE may result in superior quality of life by avoidance of severe postoperative complications and colostomy.3,9–13 Based on these reports, the practice for ARMM has gradually changed toward the less aggressive surgical intervention of LE. As part of this trend toward less invasive surgery, Brady et al44 reported, in 1995, from 64 years of experience with 56 cases in Memorial Sloan Kettering Cancer Center that APR confers better disease control, and 90% of the long-term survivors were treated with APR. However, a subsequent study by Yeh et al45 reported a paradigm shift in treatment strategy, with LE being oncologically equivalent to APR, and concluded that local recurrence and survival in ARMM are not associated with the extent of surgery.

The prognostic significance of lymph node metastasis and lymphadenectomy in the treatment of ARMM has also long been debated. Mesorectal, pelvic side wall, and inguinal lymph nodes are at increased risk for metastasis from ARMM. The oncological benefit of APR, compared with LE, is derived from the en bloc resection of mesorectal lymph nodes with the primary tumor. Therefore, APR is a validated procedure for advanced rectal cancer in terms of its local disease control contributing to favorable survival. However, in contrast to primary cutaneous melanoma, which is reported that lymph node metastasis is the most significant prognostic factor in the early
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stage,46 several studies13,31 have shown no significant prognostic impact of locoregional lymph node metastasis in ARMM. This different biological behavior compared with rectal cancer and cutaneous melanoma indicates that systemic disease dissemination occurs early, with micrometastases in distant organs associated with unfavorable survival in ARMM. Therefore, APR seems not to confer any survival advantage compared with LE. It is known that ARMM can also spread to inguinal lymph nodes, and metastasis is recognized at an advanced stage. Prophylactic inguinal lymphadenectomy in patients with nonpalpable lymph nodes does not improve survival and carries an increased risk of complications.47,48 Previous studies of small case series have recommended synchronous inguinal lymphadenectomy only when palpable lymph nodes are present.7,47 However, a recent study by Perez et al51 has reported that inguinal lymph node metastasis is not a prognostic factor in ARMM. Therefore, inguinal lymphadenectomy, even for therapeutic intent, seems not to contribute to improvement of survival.

Contrary to the idea that ARMM has already developed into a systemic rather than local disease at presentation, several studies have revealed that negative resection margins are a positive prognostic factor.22,30 Nilsson and Ragnarsson-Olding30 have reported that resection margins significantly predict long-term outcomes, with 5-year survival of 19% for patients receiving R0 resection compared with 6% for patients with R+ resection, regardless of the type of surgery. Although the current meta-analysis did not assess and could not conclude an oncological advantage of R0 compared with R1 resection, the extent of surgery did not affect survival in analyses of patients who underwent overall (R0 + R1) resection and R0 resection alone.

In general, patients undergoing APR have a worse body image and urinary dysfunction than after sphincter-saving procedures. Moreover, men are also more likely than women to suffer from sexual dysfunction after APR.49 The benefits of LE are clear and include quicker recovery from a less-invasive procedure and minimal impact on bowel function. In the absence of a clear survival benefit of one procedure over another for such an aggressive disease, quality of life for patients undergoing surgery merits consideration.30–32

It is surprising that, unlike rectal cancer, the prognosis of ARMM has not improved significantly over 30 years. Considering the limitations of disease control by surgical treatment of this aggressive disease, characterized with rapid systemic spread, development of effective supportive systemic strategies is the only hope for improved prognosis. Currently, however, no high-level evidence exists to direct the physician in the management of ARMM in the adjuvant setting, so the standard of care is observation. Recently, notable advances have been made in the understanding of in-depth molecular pathogenesis of melanoma and have translated into improved systemic treatment strategies that target the BRAF and cKIT mutations, and drugs that target the immune system, such as ipilimumab for metastatic cutaneous melanoma.53 It is known that certain mucosal melanomas, including ARMM, contain BRAF and cKIT mutations at varying rates according to anatomical site,54,55 which may predict a benefit from treatment with inhibitors of these genetic mutations in the future.

This study had several limitations that must be taken into account. Meta-analysis is recognized as an excellent tool for identifying the causes of variability and inconsistencies among studies, and the heterogeneity identified can set the stage for further research on a given hypothesis.56 However, meta-analysis may reinforce inherent systematic biases among studies and produces spurious statistical stability, thereby discouraging further research.57 The current study showed no significant heterogeneities among the analyses; however, the major limitation of this study was the current unavailability of randomized controlled trials due to the rarity of ARMM. This may have resulted in a bias for patients selected for either surgical procedure. Moreover, there were variations among the included studies in their adjuvant treatment protocol and timing of outcome assessments.

**CONCLUSIONS**

This study suggested that APR, a form of extensive surgery, has no oncological benefit in terms of patient survival; however, APR confers better local control than LE. Given that local failures after LE could be managed by salvage surgery, minimizing morbidity and maximizing quality of life should be the focus of surgical treatment of ARMM.

**ACKNOWLEDGMENTS**

The authors thank the surgical staff at the Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital, for acquisition of data.

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**TABLE 2. Subgroup Analyses for Outcomes Including OS, RFS, and Local Recurrence**

<table>
<thead>
<tr>
<th>Subgroup and Outcomes</th>
<th>No. Studies</th>
<th>No. Cases</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>Heterogeneity</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies with &gt;30 cases</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5-yr OS</td>
<td>12</td>
<td>730</td>
<td>1.17</td>
<td>0.69–2.00</td>
<td>0.56</td>
<td>36</td>
<td>0.10</td>
</tr>
<tr>
<td>5-yr RFS</td>
<td>4</td>
<td>171</td>
<td>0.69</td>
<td>0.30–1.60</td>
<td>0.39</td>
<td>0</td>
<td>0.66</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>5</td>
<td>205</td>
<td>0.11</td>
<td>0.05–0.24</td>
<td>&lt;0.00001</td>
<td>7</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Studies published after 2000</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-yr OS</td>
<td>15</td>
<td>725</td>
<td>1.04</td>
<td>0.58–1.85</td>
<td>0.90</td>
<td>39</td>
<td>0.06</td>
</tr>
<tr>
<td>5-yr RFS</td>
<td>7</td>
<td>202</td>
<td>0.71</td>
<td>0.28–1.79</td>
<td>0.46</td>
<td>12</td>
<td>0.34</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>6</td>
<td>203</td>
<td>0.19</td>
<td>0.07–0.57</td>
<td>0.003</td>
<td>46</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Studies with only R0 resection</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5-yr OS</td>
<td>20</td>
<td>603</td>
<td>1.20</td>
<td>0.73–1.98</td>
<td>0.48</td>
<td>10</td>
<td>0.33</td>
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<tr>
<td>5-yr RFS</td>
<td>9</td>
<td>207</td>
<td>1.60</td>
<td>0.60–4.26</td>
<td>0.34</td>
<td>0</td>
<td>0.55</td>
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<tr>
<td>Local recurrence</td>
<td>10</td>
<td>272</td>
<td>0.18</td>
<td>0.07–0.43</td>
<td>0.0001</td>
<td>40</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Studies originated from the United States</strong></td>
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<td></td>
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<tr>
<td>5-yr OS</td>
<td>14</td>
<td>425</td>
<td>0.97</td>
<td>0.57–1.66</td>
<td>0.92</td>
<td>0</td>
<td>0.70</td>
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<tr>
<td>5-yr RFS</td>
<td>6</td>
<td>162</td>
<td>0.88</td>
<td>0.36–2.14</td>
<td>0.77</td>
<td>0</td>
<td>0.44</td>
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<tr>
<td>Local recurrence</td>
<td>6</td>
<td>105</td>
<td>0.35</td>
<td>0.12–1.03</td>
<td>0.06</td>
<td>24</td>
<td>0.26</td>
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