Title
The Effect on Surgical Complications of Bevacizumab Added to Neoadjuvant Chemotherapy for Breast Cancer: NRG Oncology/NSABP Protocol B-40

Journal
Annals of Surgical Oncology, 24(7)

ISSN
1068-9265

Authors
Bear, Harry D
Tang, Gong
Rastogi, Priya
et al.

Publication Date
2017-07-01

DOI
10.1245/s10434-016-5662-9

Peer reviewed

Published in final edited form as:

Ann Surg Oncol. 2017 July ; 24(7): 1853–1860. doi:10.1245/s10434-016-5662-9.

The Effect on Surgical Complications of Bevacizumab Added to Neoadjuvant Chemotherapy for Breast Cancer: NRG Oncology/ NSABP Protocol B-40

Harry D. Bear, MD, PhD[1,2], **Gong Tang, PhD**[1,3], **Priya Rastogi, MD**[1,4], **Charles E. Geyer Jr., MD**[1,2], **Christine K. Zoon, MD**[2], **Kelley M. Kidwell, PhD**[1,3,5], **André Robidoux, MD**[1,6], **Luis Baez-Diaz, MD**[1,7], **Adam M. Brufsky, MD, PhD**[1,8], **Rita S. Mehta, MD**[1,9], **Louis Fehrenbacher, MD**[1,10], **James A. Young, MD**[1,11], **Francis M. Senecal, MD**[1,12], **Rakesh Gaur, MD, MPH**[1,13], **Richard G. Margolese, MD, CM**[1,14], **Paul T. Adams, MD**[1,15], **Howard M. Gross, MD**[1,16], **Joseph P. Costantino, Dr. PH**[1,3], **Soonmyung Paik, MD**[1,17], **Sandra M. Swain, MD**[1,18,19], **Eleftherios P. Mamounas, MD**[1,20], and **Norman Wolmark, MD**[1,21]

[1]NRG Oncology and the National Surgical Adjuvant Breast and Bowel Project (NSABP) (NSABP legacy trials are now part of the NRG Oncology portfolio), Pittsburgh, PA

[2]Virginia Commonwealth University, Massey Cancer Center, Richmond, VA

[3]University of Pittsburgh, Pittsburgh, PA

[4]University of Pittsburgh Cancer Institute School of Medicine, Pittsburgh, PA

[5]University of Michigan, School of Public Health, Department of Biostatistics, Ann Arbor, MI (current)

[6]Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Quebec, Canada

[7]San Juan MBCCOP, San Juan, Puerto Rico

[8]University of Pittsburgh/Magee Womens Hospital, Pittsburgh, PA

[9]University of California at Irvine, School of Medicine, Chao Family Comprehensive Cancer Center, Orange, CA

[10]Kaiser Permanente Oncology Clinical Trials Northern California, Vallejo, CA

[11]CCOP, Colorado Cancer Research Program, Colorado Springs, CO

[12]CCOP, NorthWest Medical Specialties, Tacoma, WA

[13]Kansas City Clinical Oncology Program, Kansas City, MO

Corresponding Author: Harry D. Bear, MD, PhD, Box 980011, Virginia Commonwealth University, Richmond, VA, USA 23298-0011, harry.bear@vcuhealth.org, Ph: 804-628-3242, Fx: 804-828-4808.

Clinical Trials registration: NCT00408408

Disclosures:

The following authors declare the following potential conflict(s) of interest:

CE Geyer: Non-compensated consulting: Genentech;

A Robidoux: Consulting or advisory role, and research funding: Roche Canada

SM Swain: Research to institution, Non-promotional speaking, Advisory Boards, uncompensated Steering Committees: Genentech/Roche; Advisory Board: Lilly;

EP Mamounas: Consultant and Speakers' Bureau: Genentech.

[14]Jewish General Hospital, McGill University, Montréal, QC, Canada

[15]Genesys Regional Medical Center, Grand Blanc, MI

[16]Dayton CCOP, Dayton, Ohio

[17]Severance Biomedical Science Institute and Department of Medical Oncology, Yonsei University College of Medicine, Seoul, Korea

[18]Washington Cancer Institute, Washington Hospital Center, Washington, D.C. (where the research was conducted)

[19]Georgetown University Medical Center, Washington, D.C. (current)

[20]UF Health Cancer Center at Orlando Health, Orlando, FL

[21]Allegheny Health Network Cancer Institute, Pittsburgh, PA

Abstract

Background—NRG Oncology/NSABP trial B-40 tested the impact of adding bevacizumab (bev) to neoadjuvant chemotherapy for operable breast cancer. Secondary endpoints included rates of surgical complications after surgery in patients who did or did not receive bev.

Methods—1206 women with HER2-negative operable breast cancer were randomly assigned to receive one of three different docetaxel-plus-anthracycline-based regimens, without or with bev (15mg/kg every 3 weeks) for the first 6 of 8 cycles and for 10 doses postoperatively. Surgical complications were assessed from date of surgery through 24 months following study entry.

Results—Early surgical complications were significantly more frequent in the bev group (25.4% vs. 18.9%; trend test p=0.008), but most were grade 1–2. Early noninfectious wound dehiscences were infrequent and not significantly different (5.4% vs. 3.1%; trend test p=0.15). Long-term noninfectious wound complications were significantly higher for patients receiving bev (11.8% vs. 5.1%; trend test p=0.0007), but the incidence of grade ≥3 wound dehiscence was low in both groups (<1%). Among 193 patients undergoing expander or implant reconstructions, 19 (19.6%) of 97 in the bev-receiving group versus 10 (10.4%) of 96 in the non-bev group had grade ≥3 complications (Pearson p=0.11).

Conclusions—Overall, adding bev increased surgical complications, but most serious complications were not significantly increased. In particular, the need for surgical intervention in patients undergoing breast reconstruction with prosthetic implants was higher with bev, but was not statistically significantly different. With precautions, bev can safely be used peri-operatively in patients undergoing surgery for breast cancer.

Keywords

Bevacizumab; breast cancer; neoadjuvant; surgery; complications

INTRODUCTION

Anti-angiogenic compounds were predicted to have anti-tumor effects by Folkman and others[1] more than four decades ago. By inhibiting and even reversing new blood vessel

formation in the tumor microenvironment, such agents potentially could deprive cancer cells of oxygen and nutrients and, by "normalizing" tumor vasculature, could possibly improve delivery of cytotoxic agents.[1,2] The humanized monoclonal antibody to vascular endothelial growth factor A (VEGF), bevacizumab (bev), has clinical activity against a variety of cancer types, including glioblastoma and colorectal, breast, and lung cancer.[3–6]

However, inhibition of blood vessel formation via bev or other anti-angiogenic agents can impair wound healing.[7–12] Based on the 20-day half-life of bev and the biology of wound healing, it has been recommended that elective surgery be delayed 4–8 weeks after the last dose of bev and that bev should be started or resumed 2–4 weeks after surgery.13–15, [a] This concern has been raised for patients with metastatic colorectal cancer who are candidates for liver resection after a period of chemotherapy plus bev. However, with judicious timing of surgery, an increased risk of wound complications has not been consistently reported.[16–19] Conversely, there have been observations of increased incidence of wound breakdown after craniotomies and port placements for patients who had received or subsequently were treated with bev.[20–22] However, none of these data have come from randomized controlled trials. In two prospective trials of bev for metastatic breast cancer (AVADO and ATHENA), statistically significant increases in wound complications were not observed in patients receiving this agent and undergoing surgery.[23] However, not all patients in these trials had surgery, and many of the surgical procedures were neither major nor directed at the breast primary tumors.

Concerns have been raised for patients undergoing breast surgery after neoadjuvant chemotherapy (NCT) including bev, especially for women who undergo mastectomy with reconstruction. In one retrospective study, more implants placed for reconstruction were removed in the bev group than in the non-bev group, but there was no statistically significant difference in overall wound complications.[24] A later retrospective report,[25] using matched controls who received NCT without bev, also found no difference in overall wound complication rates (32% versus 31%), but indicated that 30% of women with implant reconstructions after bev had complications, and two with wound breakdown lost implants. The National Surgical Adjuvant Breast and Bowel Project (NSABP) undertook a prospective randomized trial of NCT with or without bev for women with stage II–III operable breast cancer, accruing 1206 patients from 2007–2010. Patients randomly assigned to receive bev preoperatively were also to receive bev for 30 weeks postoperatively. The results, in terms of tumor response, early wound complication rates, and long-term outcomes, have been reported previously.[26, 27] However, with the concerns outlined above, we sought to examine the relative rates of both early and late surgical complications in more detail. This is the first study to evaluate the short- and long-term complication rates in a large prospective trial in patients randomly assigned to NCT without bev versus those assigned to NCT plus bev, with bev administered both pre- and postoperatively.

[a]Current USPI labelling for bev states: "Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed."

METHODS

These trials were approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services. Written informed consent was required for participation.

Trial design

Our primary hypotheses were that addition of capecitabine, gemcitabine, and/or bev to NCT would increase pathologic complete response (pCR) rates in the breast for women with operable HER2-nonamplified breast cancer. Surgical complication was a pre-specified secondary endpoint. Key eligibility requirements included palpable primary breast tumors, clinical stage T1c (if 2.0 cm), T2 or T3, and N0-N2a, M0; ECOG performance status of 0 or 1, and normal cardiac function. Patients were randomly assigned to receive either docetaxel, capecitabine plus docetaxel, or gemcitabine plus docetaxel every 3 weeks for 4 cycles, followed by doxorubicin plus cyclophosphamide every 3 weeks for 4 cycles. Additionally, half were randomly assigned to receive or not to receive bev (15 mg/kg) on day 1 of each of the first 6 cycles of chemotherapy. In order to minimize risk of operative morbidity, bev was stopped after cycle 6 to allow at least a 9-week “washout” period before surgery. For patients who stopped treatment early for any reason, it was advised that surgery be delayed 4–6 weeks from the last dose of bev. The choice of breast-conserving surgery (BCS) versus mastectomy was at investigator discretion, as was the decision to perform immediate reconstruction. However, if tissue expanders were used, no expansion was allowed beyond 2 weeks prior to the first postoperative dose of bev, and no expansions or elective surgery was allowed throughout the course of bev therapy, which was intended to be 10 doses at 3-week intervals. Breast radiotherapy was required for patients undergoing BCS; the addition of regional-nodal irradiation or post-mastectomy radiotherapy was at the treating physician’s discretion.

Breast reconstruction and late surgical complications data were collected by submission of additional case report forms from each participating site. Data were collected on all surgical complications as well as on infections and noninfectious wound complications from surgery to 3–5 weeks following surgery, and from the previous time interval to 9, 12, and 24 months following entry. We initially used CTCAE, v3.0 to grade the severity of all complications, but early in the trial switched to CTCAE, v4.0 (Table). Early complications were defined as those occurring 3–5 weeks from the date of surgery, and those occurring later were defined as late complications.

Statistical Methods

Contingency table analyses were performed to estimate the proportion of surgical complications over time and to compare the surgical complications between the bev and non-bev groups in all eligible patients or those who had ever had breast reconstruction. Both the Pearson Chi-square test with continuity correction and the Cochran-Armitage trend test were performed in the comparisons.[28] A test result was considered statistically significant if the corresponding p-value was ≤0.05.

RESULTS

Early complications

Among 1206 patients randomly assigned in the NSABP B-40 study, 1183 were eligible and 1157 (579 in the bev group, 578 in the non-bev group) underwent breast surgery. Among those 1157 patients, 1154 (577 in each group) had assessment of post-op surgical complications. At 3–5 weeks after surgery, 1122 had assessment of surgical complications (560 in the bev group, 562 in the non-bev group). Overall highest grades of surgical complications are shown in Fig 1a and the Supplementary Table. The rate of early complications was statistically significantly higher in the bev group (Pearson p=0.22; trend test p=0.008). However, rates of early noninfectious surgical complications were not statistically significantly different between groups (Fig 1b) (Pearson p=0.51, trend test p=0.15). Except for hematomas, seromas and wound infections of all grades were also not statistically significantly different for patients receiving or not receiving bev (4.8% vs. 2.3% for hematomas [Pearson p=0.04], 14.3% vs. 12.3% for seromas, and 3.6% vs. 2.3% for wound infections).

Longer-term complications after surgery

Overall highest grades of surgical complications at all time points and at 9, 12, and 24 months after study entry are shown in Fig. 2a–d and the Supplementary Table. At all timepoints, the incidence of complications was statistically significantly higher for patients receiving bev, but most were mild (grades 1–2). The incidence of noninfectious wound dehiscence overall and at later time points is shown in Fig 3a–d. The rate of these events was statistically significantly higher overall and at 9 and 12 months (trend test p=0.0007, 0.007, and 0.0001). However, at all timepoints, the incidence of serious (grade≥3) wound dehiscence was quite low in both groups (<1%). Results from multivariate logistic regression models showed that the incidence of serious (grade≥3) surgical complications was higher in patients randomized to bev (OR=1.96, 95%CI=1.24, 3.15; p=0.005) and in patients who underwent mastectomy (OR=3.20, 95%CI=1.90, 5.63; p<0.001). Receiving radiotherapy was not associated with a higher incidence (p=0.64). There was no interaction between bev and the type of surgery (p=0.87) or between bev and radiotherapy (p=0.69). Patients assigned to bev had a higher incidence of any surgical complication (OR=1.65, 95%CI=1.29, 2.12; p<0.001). There was no evidence showing varying incidence of any surgical complication between surgery groups (p=0.16) and choice of radiotherapy (p=0.64).

Among the 573 patients with treatment data for administration of post-op bev doses, 147 (25.7%) did not start bev postoperatively, 103 (18%) received 1–6 doses, 36 (6.3%) received 7–9, and 287 (50.1%) received 10–11. Grade 3–4 complications were reported in 18 of the 147 (12.2%) who only received pre-op bev. Among the 426 who received at least 1 dose of post-op bev, 36 (8.5%) had grade 3–4 complications.

A similar proportion of patients in each treatment group underwent mastectomies: Bev: 305 (53%)/577, Non-bev: 315 (55%) of 577. Overall surgical complications were consistently higher in the bev group among those 620 patients (Pearson p=0.003), trend test p=0.002) and among the other 534 who underwent lumpectomies (Pearson p=0.005), trend test p=0.002).

Specific wound complications in patients who underwent reconstruction

Among the 620 patients with mastectomies, data on breast reconstruction were submitted from 612 (Bev: 300, Non-bev: 312). Similar proportions underwent breast reconstruction: 124 (41%) of 300 in the bev group and 130 (42%) of 312 in the non-bev group (Fig. 4a). There was no statistically significant difference in the types of breast reconstruction between the two arms (Pearson p=0.50, 0.86, 1, and 0.14, respectively) (Fig. 4b). Overall rates of surgical complication (at any time up to 24 months after study entry) in patients undergoing reconstruction are shown in Fig. 4c. Rates of surgical complications were statistically significantly higher in patients receiving bev (Pearson p=0.36, trend test p=0.03). Mostly, the increase in complications among bev patients was accounted for by seromas (17.7% versus 10% Pearson p=0.11, OR=1.94[0.88–4.41]) and wound dehiscence (19.3% versus 11.5%, p=0.12, OR=1.84[0.87, 3.99]). With all types of reconstruction, rates of serious wound complications (grades 2–4) were 34.7% for the bev group versus 24.6% for the non-bev group (Pearson p=0.11, OR=1.62[0.91–2.91]), and those requiring surgical intervention (ie, grade ≥3) were 17.7% versus 10% (Pearson p=0.11, OR=1.94[0.88–4.41]). Among 193 patients who underwent expander or implant reconstructions, 29 (15%) had grade ≥3 complications: 19 (19.6%) of 97 in the bev group and 10 (10.4%) of 96 in the non-bev group (Pearson p=0.11, OR=2.09[0.86, 5.35]). Regression analysis showed that patients with breast implants or expanders had incidence of surgical complications similar to those who had rotated or free flaps (p=0.92).

Of the 620 patients who underwent mastectomy, 432 (69.7%) had post-mastectomy radiotherapy, 178 did not, and no information on the use of radiotherapy was available from the other 10. Among those 432 who received radiotherapy, 47 (10.9%) had grade 3–4 complications: 29 (13.7%) among 211 bev patients and 18 (8.1%) among 221 non-bev patients (Pearson p=0.09). Of those 178 who did not receive radiotherapy, 18 (10.1%) experienced grade 3–4 complications: 12 (13.8%) of 87 bev patients and 6 (6.6%) of 91 non-bev patients (Pearson p=0.18).

Results from logistic regression models suggested that, among patients with mastectomy, the incidence of serious (grade ≥3) surgical complications was higher in those randomized to bev (OR=2.02, 95%CI=1.19, 3.52; p=0.01) and in those who underwent breast reconstruction (OR=1.80, 95%CI =1.06, 3.08; p=0.03). The incidence of any surgical complication was higher in patients randomized to bev (OR=1.91, 95%CI=1.35, 2.71; p=0.0003) but was related to neither breast reconstruction (p=0.16) nor to radiotherapy (p=0.41).

DISCUSSION

With the advent of therapeutic agents that inhibit angiogenesis, there has been concern that using such drugs in the perioperative period might increase the rates of surgical complications, particularly wound healing. This concern has been increased because of the more frequent use of systemic therapy before and immediately after surgery. Of particular concern has been the compromise of wounds that are being subjected to increased tension because of implantation and expansion of prosthetic tissue expanders used in breast reconstruction. For this reason, the NSABP B-40 protocol incorporated a number of

safeguards regarding the use of these devices. In spite of these precautions, there was a statistically significant increase in overall surgical complications in patients who were assigned to bev. Among those who underwent prosthetic reconstruction after mastectomy, 19.6% suffered grade ≥3 wound complications, requiring surgical intervention, compared to 10.4% for the non-bev group. However, this was not a statistically significant difference. Even though there was a statistically non-significant increase in dehiscences, the precautions built into this protocol should serve as useful guidelines for subsequent breast cancer patients receiving antiangiogenic therapy in the perioperative period.

The potential relevance of these findings to the care of future breast cancer patients is uncertain because of the conflicting results regarding the benefit of adding bev to chemotherapy for breast cancer.[6] Despite improvements in progression-free survival for patients with metastatic disease, improvements in overall survival (OS) did not materialize, and trials of bev added to adjuvant chemotherapy were negative.[29–34] In the neoadjuvant setting, some trials showed improvements in pCR rates with added bev, particularly for triple-negative breast cancers, but this did not translate into long-term benefits in terms of disease-free survival or OS.[35–37] However, a recently reported randomized trial demonstrated an increase in pCR, as well as a trend toward improved event-free survival with the addition of bev to NCT for locally advanced and inflammatory triple-negative breast cancer.[38]

In contrast, the B-40 trial demonstrated increased pCR rates with bev, preferentially in hormone-receptor positive breast cancer, and there was also an increase in OS for those who received bev.[26,27] Nevertheless, because of the inconsistent results with this drug, the results of B-40 are not likely to change practice. However, B-40 was unique in that bev was given both before and after surgery. Future studies taking advantage of the tumor biopsies that were collected for research prior to treatment in this study may define a subset of patients who more clearly derive benefit from the addition of bev to NCT. If so, then this may result in the incorporation of bev in certain patients, and then the data presented here will certainly be relevant. Even if bev does not become used in the therapy of breast cancer, the findings reported here provide important insights relative to surgical complications that may be relevant for cancers such as those of the colon, lung, ovary, cervix, and kidney, and for glioblastoma multiforme, for all of which this drug is now commonly used.

CONCLUSIONS

This is the first report of a large, prospective randomized trial evaluating the short- and long-term complication rates from surgery in patients randomly assigned to receive or not to receive bevacizumab as neoadjuvant and adjuvant therapy. Despite the overall increase in surgical complications with the addition of bev, serious complications were, for the most part, not statistically significantly increased. In particular, the need for surgical intervention in patients undergoing breast reconstruction with prosthetic implants was higher, but not statistically significantly different. With appropriate precautions, the risks of breast surgery, with or without reconstruction, should not bar the use of bev for patients with breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

HDB and GT had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

This work was supported by: National Cancer Institute, Department of Health and Human Services, Public Health Service Grants: U10-CA-108068, U10-CA-180822, NCI-44066-26(AR); UG1CA-189867, UM1-CA-189869(HDB), and UGI-CA-189853(RG) (NCORPs); and by Genentech, Inc., a full member of the Roche Group of companies; Roche Laboratories Inc.; Lilly Research Laboratories, a division of Eli Lilly & Company; and Precision Therapeutics, Inc.

We also thank participating member sites as well as patients enrolled in the study.

References

1. Folkman J. Tumor angiogenesis: Therapeutic implications. N Engl J Med. 1971; 285:1182–6. [PubMed: 4938153]
2. Holleb AI, Folkman J. Tumor angiogenesis. CA Cancer J Clin. 1972; 22:226–9. [PubMed: 4625047]
3. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993; 362:841–4. [PubMed: 7683111]
4. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 1997; 57:4593–9. [PubMed: 9377574]
5. Stevenson CE, Nagahashi M, Ramachandran S, Yamada A, Bear HD, Takabe K. Bevacizumab and breast cancer: What does the future hold? Future Oncol. 2012; 8:403–14. [PubMed: 22515444]
6. Kümler I, Christiansen OG, Nielsen DL. A systematic review of bevacizumab efficacy in breast cancer. Cancer Treat Rev. 2014; 40:960–73. [PubMed: 24909311]
7. Ladha H, Pawar T, Gilbert MR, et al. Wound healing complications in brain tumor patients on bevacizumab. J Neurooncol. 2015; 124:501–6. [PubMed: 26298437]
8. Keating GM. Bevacizumab: A review of its use in advanced cancer. Drugs. 2014; 74:1891–925. [PubMed: 25315029]
9. Eveno C, Passot G, Goéré D, et al. Bevacizumab doubles the early postoperative complication rate after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2014; 21:1792–800. [PubMed: 24337648]
10. Sharma K, Marcus JR. Bevacizumab and wound-healing complications: Mechanisms of action, clinical evidence, and management recommendations for the plastic surgeon. Ann Plast Surg. 2013; 71:434–40. [PubMed: 22868316]
11. Yardley DA, Raefsky E, Castillo R, et al. Phase II study of neoadjuvant weekly nab-paclitaxel and carboplatin, with bevacizumab and trastuzumab, as treatment for women with locally advanced HER2+ breast cancer. Clin Breast Cancer. 2011; 11:297–305. [PubMed: 21729666]
12. Koskas M, Chereau E, Ballester M, Selle F, Rouzier R, Daraï E. Wound complications after bevacizumab treatment in patients operated on for ovarian cancer. Anticancer Res. 2010; 30:4743–7. [PubMed: 21115934]
13. Abrams DA, Hanson JA, Brown JM, Hsu FP, Delashaw JB Jr, Bota DA. Timing of surgery and bevacizumab therapy in neurosurgical patients with recurrent high grade glioma. J Clin Neurosci. 2015; 22:35–9. [PubMed: 25481268]
14. Bose D, Meric-Bernstam F, Hofstetter W, Reardon DA, Flaherty KT, Ellis LM. Vascular endothelial growth factor targeted therapy in the perioperative setting: Implications for patient care. Lancet Oncol. 2010; 11:373–82. [PubMed: 20171141]
15. Gordon CR, Rojavin Y, Patel M, et al. A review on bevacizumab and surgical wound healing: An important warning to all surgeons. Ann Plast Surg. 2009; 62:707–9. [PubMed: 19461291]

16. Neeff HP, Drognitz O, Klock A, et al. Impact of preoperative targeted therapy on postoperative complications after resection of colorectal liver metastases. Int J Colorectal Dis. 2012; 27:635–45. [PubMed: 22139030]
17. Hompes D, Ruers T. Review: Incidence and clinical significance of bevacizumab-related non-surgical and surgical serious adverse events in metastatic colorectal cancer. Eur J Surg Oncol. 2011; 37:737–46. [PubMed: 21764243]
18. Mahfud M, Breitenstein S, El-Badry AM, et al. Impact of preoperative bevacizumab on complications after resection of colorectal liver metastases: Case-matched control study. World J Surg. 2010; 34:92–100. [PubMed: 19838754]
19. Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. J Clin Oncol. 2008; 26:5254–60. [PubMed: 18854565]
20. Golas AR, Boyko T, Schwartz TH, Stieg PE, Boockvar JA, Spector JA. Prophylactic plastic surgery closure of neurosurgical scalp incisions reduces the incidence of wound complications in previously-operated patients treated with bevacizumab (Avastin®) and radiation. J Neurooncol. 2014; 119:327–31. [PubMed: 24872117]
21. Kriegel I, Cottu PH, Fourchotte V, et al. Wound healing and catheter thrombosis after implantable venous access device placement in 266 breast cancers treated with bevacizumab therapy. Anticancer Drugs. 2011; 22:1020–3. [PubMed: 21970853]
22. Erinjeri JP, Fong AJ, Kemeny NE, Brown KT, Getrajdman GI, Solomon SB. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. Cancer. 2011; 117:1296–301. [PubMed: 21381016]
23. Cortés J, Caralt M, Delaloge S, et al. Safety of bevacizumab in metastatic breast cancer patients undergoing surgery. Eur J Cancer. 2012; 48:475–81. [PubMed: 22196033]
24. Golshan M, Garber JE, Gelman R, et al. Does neoadjuvant bevacizumab increase surgical complications in breast surgery? Ann Surg Oncol. 2011; 18:733–7. [PubMed: 20882415]
25. Kansal KJ, Dominici LS, Tolaney, et al. Neoadjuvant bevacizumab: Surgical complications of mastectomy with and without reconstruction. Breast Cancer Res Treat. 2013; 141:255–9. [PubMed: 24026859]
26. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med. 2012; 366:310–20. [PubMed: 22276821]
27. Bear HD, Tang G, Rastogi P, et al. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): Secondary outcomes of a phase 3, randomised controlled trial. Lancet Oncol. 2015; 16:1037–48. Erratum in: Lancet Oncol, 2015, 16: e589. [PubMed: 26272770]
28. Agresti, Alan. Categorical Data Analysis. 2. Wiley; 2002. https://mathdept.iut.ac.ir/sites/mathdept.iut.ac.ir/files/AGRESTI.PDF [Accessed 8-8-16]
29. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without Bev for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011; 29:1252–60. [PubMed: 21383283]
30. Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2010; 28:3239–47. [PubMed: 20498403]
31. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007; 357:2666–76. [PubMed: 18160686]
32. Miller K, O'Neill AM, Dang CT, et al. Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: Final results from Eastern Cooperative Oncology Group E5103. J Clin Oncol. 2014; 32:500.
33. Slamon DJ, Swain SM, Buyse M, et al. Primary results from BETH, a phase 3 controlled study of adjuvant chemotherapy and trastuzumab ± bevacizumab in patients with HER2-positive, node positive or high risk node-negative breast cancer. Cancer Res. 2013; 73:S01–03.
34. Cameron D, Brown J, Dent R, et al. Adjuvant bevacizumab containing therapy in triple-negative breast cancer (BEATRICE): Primary results of a randomised, phase 3 trial. Lancet Oncol. 2013; 14:933–42. [PubMed: 23932548]

35. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; Results from the Geparquinto study (GBG44). Ann Oncol. 2013; 24:2978–84. [PubMed: 24136883]

36. von Minckwitz G, Loibl S, Untch M, et al. Survival after neoadjuvant chemotherapy with or without bevacizumab or everolimus for HER2-negative primary breast cancer (GBG 44 - - GeparQuinto). Ann Oncol. 2014; 25:2363–72. [PubMed: 25223482]

37. Sikov W, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/− carboplatin and/or bevacizumab in triple-negative breast cancer: Outcomes from CALGB 40603 (Alliance). 2015 Abstr S2-05, SABCS.

38. Nahleh ZA, Barlow WE, Hayes DF, et al. SWOG S0800 (NCI CDR0000636131): addition of bevacizumab to neoadjuvant nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide improves pathologic complete response (pCR) rated in inflammatory or locally advanced breast cancer. Breast Cancer Res Treat. 2016; 158:485–495. [PubMed: 27393622]

Synopsis

In a large randomized trial, the addition of neoadjuvant and adjuvant bevacizumab to neoadjuvant chemotherapy for breast cancer statistically significantly increased the overall surgical complication rate. However, with appropriate safeguards, serious complications requiring surgical intervention were not increased significantly.

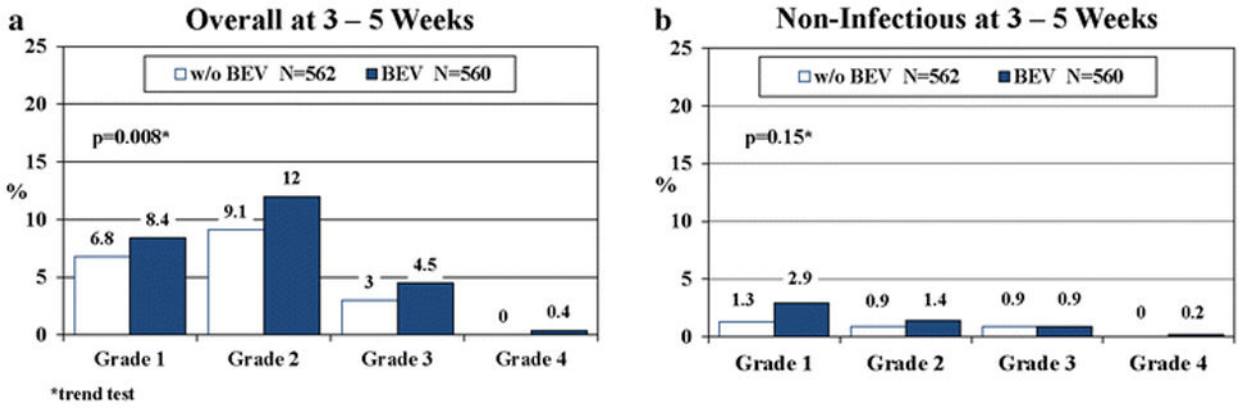

FIG. 1.

Overall highest grades with or without bevacizumab (bev) at 3–5 weeks after surgery **(a)** surgical complications, **(b)** non-infectious surgical complications.

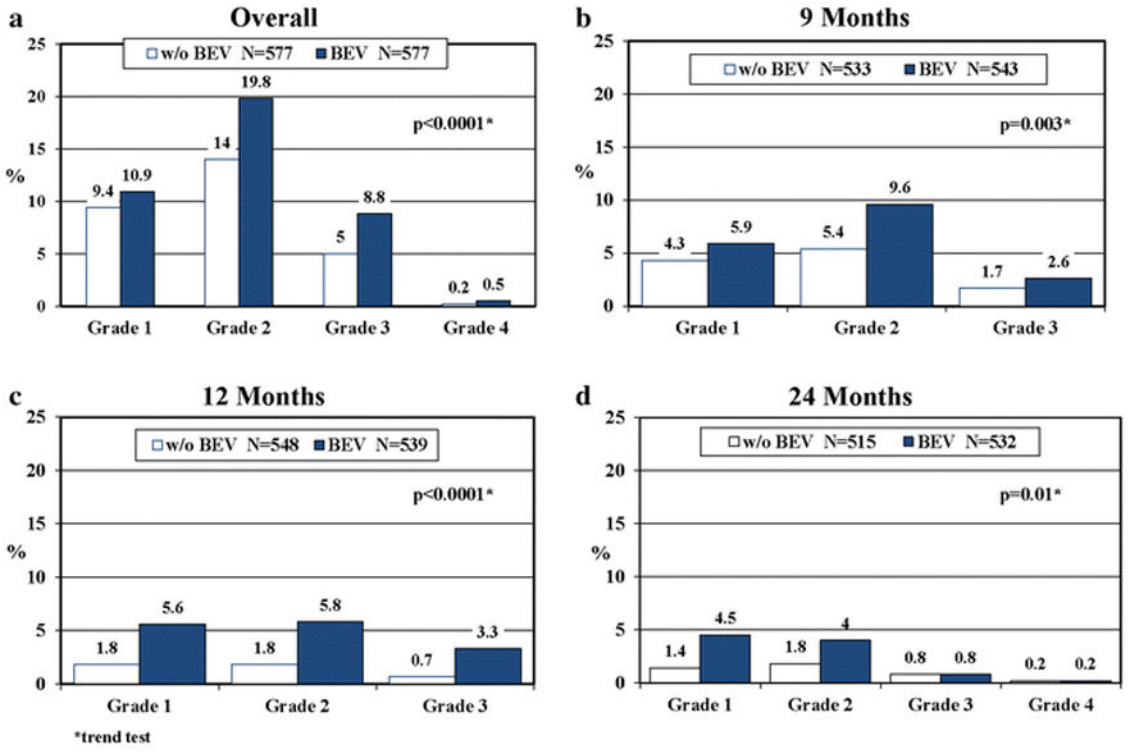

FIG. 2.

Overall highest grades of surgical complications, with or without bevacizumab (bev), **(a)** at all time points, **(b)** at 9 months, **(c)** at 12 months, and **(d)** at 24 months.

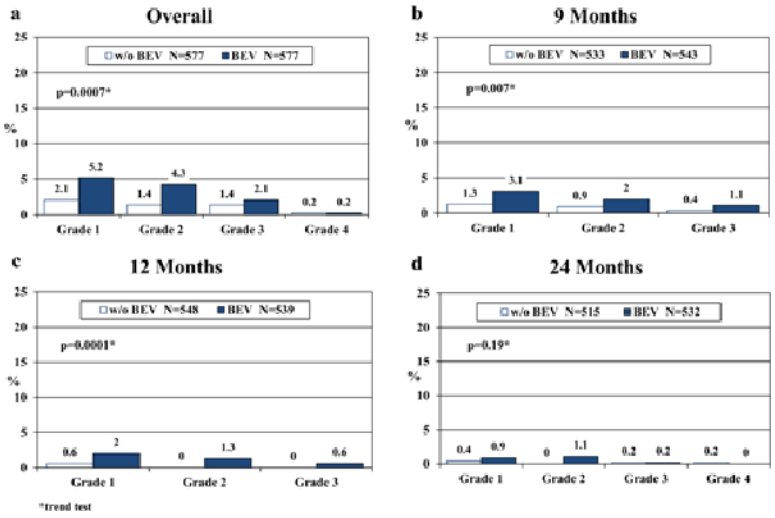

FIG. 3.

Incidence of non-infectious wound dehiscences, with or without bevacizumab (bev), **(a)** at all time points**, (b)** at 9 months**, (c)** at 12 months**,** and **(d)** at 24 months.

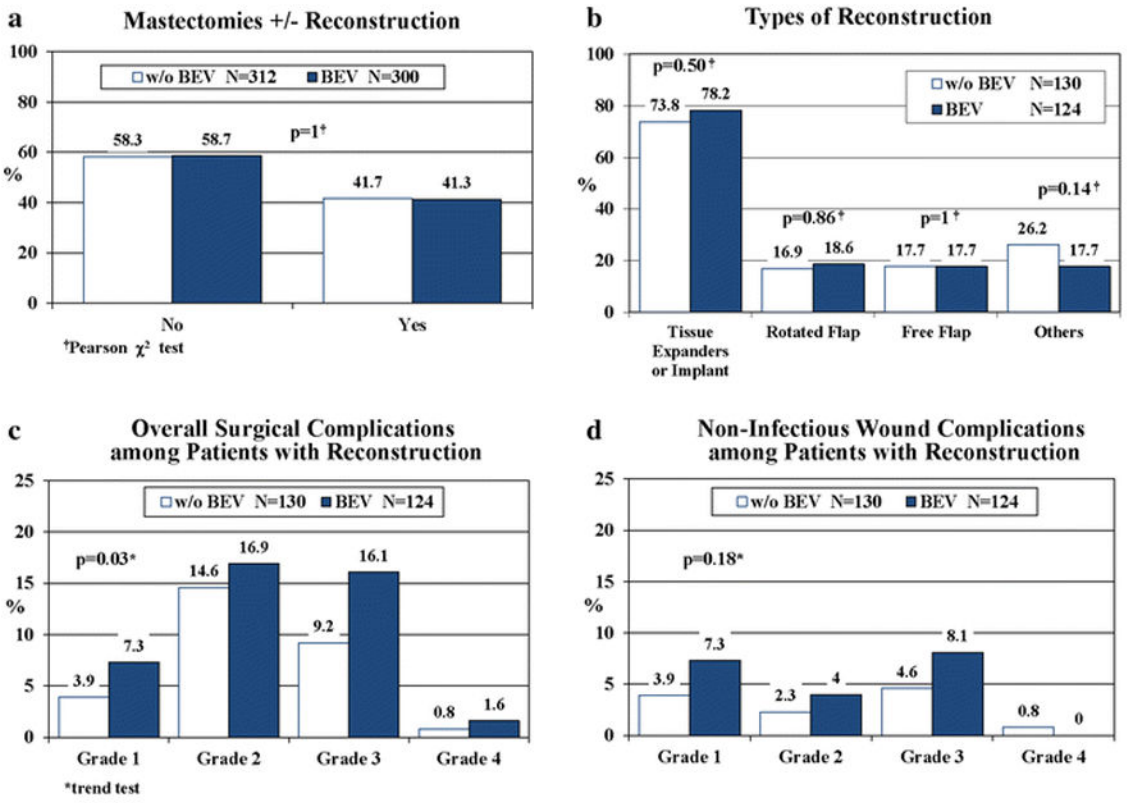

FIG. 4.

(a) Proportions of patients who did or did not undergo reconstruction after total mastectomy in those with bevacizumab (bev) and without bev.

(b) Proportions of patients who underwent different types of reconstruction procedures in those with bev and without bev.

Overall rates of **(c)** surgical complications, and **(d)** non-infectious surgical complications, by highest grade, among patients with bev and without bev who underwent reconstruction.

TABLE 1

CTCAE 4.0 Wound dehiscence grading

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Wound dehiscence	Incisional separation of ≤25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Fascial disruption or dehiscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death

REMARK: Wound dehiscence is defined as a finding of separation of the approximated margins of a surgical wound.

Source: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. June 14, 2010 (http://ctep.cancer.gov), Publish Date: June 14, 2010.