RESEARCH ARTICLE

# Is Preoperative Bevacizumab Associated with Increased Complications After Urgent Hip Fracture Surgery? A Retrospective Review

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## Abstract

**Objectives:** To investigate whether patients with impending or completed fracture of the proximal femur who were treated with bevacizumab in the six weeks prior to surgery are at higher risk of surgical complications than patients given bevacizumab outside of the six-week period.

**Methods:** We retrospectively reviewed cases of hip fracture treated between 1995 and 2020 at our institution. Patients were included if they were age 18 years or older, underwent hip surgery for impending or completed fracture, and received bevacizumab preoperatively but not postoperatively. Charts were reviewed for demographic, surgical, and postoperative details. A Cox model was applied to assess whether the timing of preoperative bevacizumab administration (≤6 weeks vs. >6 weeks) was associated with the risk of a postoperative complication.

**Results:** Two of the 23 patients who received bevacizumab ≤6 weeks before surgery experienced complications (deep vein thrombosis [n=1] and intraoperative fracture related to progression of disease [n=1]). Of the 53 patients who received bevacizumab more than six weeks preoperatively, five experienced complications (wound drainage [n=2] and deep vein thrombosis [n=3]). In the Cox model, timing of bevacizumab was not associated with postoperative complications (univariable hazard ratio, 0.92; 95% confidence interval, 0.18–4.73).

**Conclusion:** In this cohort of patients who underwent surgery for hip fractures, we did not observe an increased risk of postoperative complications among those who received bevacizumab within six weeks of surgery relative to those who received bevacizumab more than six weeks before surgery. The retrospective nature of the study and small sample size are limiting factors in this study.

**Level of evidence:** III

**Keywords:** Bevacizumab, Hip fracture surgery, Wound complications

## Introduction

The hip joint and the proximal femur are common sites for metastatic disease to bone.[1] The presence of tumor in this vital weight-bearing zone can result in severe pain upon standing or walking. Such functional pain, in combination with relevant imaging features (e.g., changes in mineralization, increased lesion size, cortical thinning and/or breakthrough), is predictive of fracture risk.[2] These impending fractures may require surgical stabilization, and completed fractures require that stabilization be done without delay.[3]

Even in the absence of metastatic disease, hip fractures are serious injuries that can lead to immobility and disability, negatively impacting the patient's quality of life and resulting in a financial burden for both the health care system and society.[4] Mortality rates among the elderly following hip fracture range from 14% to 36% within one year of the injury, and the mortality risk remains elevated for up to 10 years.[5]

Surgical intervention for hip fracture has proven to be highly effective.[6] However, in cases of impending pathologic fracture, determining the optimal timing for surgery becomes more complex and depends on the level of functional disability imposed by the condition as well as the level of fracture risk. In some instances, delaying surgical

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intervention for several weeks may not be feasible due to the risks associated with prolonged immobility and the potential for complications.[7]

Many patients with metastatic disease to bone are on systemic therapy, such as chemotherapy or immunotherapy. Systemic therapies may impair wound healing, especially when administered close to the date of surgery. Physicians must balance the urgent need to give life-saving systemic therapy against the risk of perioperative complications. In the case of elective surgeries, these therapies often can be suspended temporarily; however, this is rarely an option in the case of urgent and/or emergency surgery.

There is a paucity of data guiding the timing of systemic cancer therapy relative to surgery to optimize wound healing. In prior work, we reviewed commonly used systemic cancer drugs and found that only 11 (9%) of 118 commonly used systemic cancer therapies had an official recommendation regarding the timing of perioperative administration: 0 of 75 chemotherapy drugs, 11 (41%) of 27 targeted therapy drugs, 0 of 9 hormonal therapy drugs, and 0 of 7 immunotherapy drugs.[8] However, most existing recommendations suggest withholding the relevant drug for 4–6 weeks before elective surgery and 3–8 weeks after the procedure.[9-11]

Many systemic therapies exert their effects by inhibiting cell metabolism, cell division, and/or angiogenesis. Consequently, they can delay wound healing by halting the inflammation process, impeding angiogenesis and cell migration to the wound site, and reducing collagen production through the inhibition of fibroblast proliferation. Additionally, these medications can increase the risk of wound infections by compromising the function of immune cells, such as neutrophils.[12]

Bevacizumab, also known as Avastin, is a monoclonal antibody against vascular endothelial growth factor (VEGF) and was approved by the U.S. Food and Drug Administration for the treatment of metastatic breast cancer, metastatic colorectal cancer, metastatic non–small cell lung cancer, metastatic renal cell cancer, and glioblastoma multiform.[13] Through its inhibition of VEGF, bevacizumab serves as an antiangiogenic agent and mediates normal physiological processes that can lead to such adverse effects as hypertension, hemorrhage, and arterial thromboembolism. However, because angiogenesis is crucial for wound healing, bevacizumab is one of many cancer therapy drugs (and among the best known of these drugs) whose use can impair wound healing.[14] Perioperative bevacizumab use has been linked to impaired wound healing in patients undergoing colorectal, breast, and brain surgeries,[14,15] and delayed wound healing has been documented even with small incisions, such as with the placement of a chest wall port, within two weeks of bevacizumab administration.[16] Its long half-life (which averages 21 days, but can range from 10 to 50 days[17]) leads to a long period of increased risk. The increasing utilization of bevacizumab has resulted in a higher incidence of wound healing issues in some patient populations. Because the drug's average half-life is 3 weeks, discontinuing bevacizumab 6 weeks before surgery allows the blood concentration to decrease to a level that is not expected to impair healing.[18] Hurwitz et al. reported that the risk of complications significantly decreased when elective surgery was postponed for at least 6 weeks following completion of bevacizumab therapy.[19] Scappaticci et al. found that the rate of wound complications in patients who underwent urgent surgery while using bevacizumab was substantially higher than in those who had cancer surgery 4–8 weeks before starting bevacizumab (13% vs. 3%).[15]

When patients experience wound healing problems while using bevacizumab, it can be necessary to discontinue the medication and provide wound care for four to six weeks. Once the wound has healed, bevacizumab may be resumed.[14]

Despite the growing literature on this issue, little is known about the risks of bevacizumab among patients with cancer who have completed or impending hip fractures. These individuals have an urgent need for surgery to prevent local and systemic complications related to immobilization, and therefore cannot safely wait for weeks, or even many days, to have surgery. Hip fracture surgery in metastatic disease is unique in that the goal of stabilization of the fracture and/or arthroplasty is to provide immediate stability, so that surgeons do not rely on bony healing for successful outcomes. Nonetheless, wound healing is a critical aspect of surgery, and this process may be at risk with concomitant administration of bevacizumab.

Therefore, we sought to investigate if patients with impending or completed fracture of the proximal femur who were treated with bevacizumab in the six weeks prior to surgery are at higher risk of wound and other complications compared to patients given bevacizumab outside the six-week period. We hypothesized that the rate of complications would be greater if bevacizumab recipients had been treated with the drug within the six-week preoperative window.

## Materials and Methods

We performed a retrospective review of 2,357 patients who underwent surgery for completed fracture or impending fracture of the proximal femur at our institution from January 1, 1995 to February 1, 2020. Patients were included in the analysis if they were age 18 years or older, had undergone primary hip fracture surgery (arthroplasty or internal fixation), and had received bevacizumab before surgery; they were excluded if they had received bevacizumab after surgery (regardless of presurgical use). The resulting sample consisted of 76 patients who received bevacizumab before hip fracture surgery.

For each eligible patient, we performed a chart review that covered all follow-up visits. We collected evidence of wound complications, including wound drainage, dehiscence, superficial or deep infection, and whether a return to the operating room was required. We also looked for evidence of other complications, such as fracture, hardware failure and deep vein thrombosis. We compiled data on demographic and clinical variables, including patient age, gender, primary histology, disease state (localized versus metastatic), fracture type, and whether the surgery was related to metastatic disease or noncancerous indications. Finally, we recorded information on additional clinical factors, such as whether the fracture was displaced, if radiation was received perioperatively, and whether

negative pressure wound dressings wound dressings were used.

Descriptive statistics were used to summarize the patient and surgical characteristics. The number of patients with a complication is reported based on the timing of preoperative bevacizumab administration, both overall and among patients who underwent arthroplasty. We used a univariable Cox model to assess whether the timing of preoperative bevacizumab use (categorized as ≤6 weeks or >6 weeks) was associated with the cause-specific hazard of a postoperative complication. Patients with a complication (wound healing or other) were considered to have an event; those who died without a complication or were alive without a complication at the end of follow-up were censored. We report results of the Cox model as hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were performed in R v4.1.2 (R Foundation for Statistical Computing). This study was approved by our institutional review board (IRB number #20-102) and was compliant with the 1964 Declaration of Helsinki.

## Results

The 76 patients in our analytic sample ranged in age from 27 to 87 years, with a median of 65 years (interquartile range, 54–71) [Table 1]. Sixty-six percent were female. Lung cancer was the most common histology. Thirty patients (30%) had received radiation therapy. Forty-nine patients (64%) had a displaced fracture. Arthroplasty accounted for 80% of the surgeries, while 20% were internal fixations. Among patients who were alive without a complication, the median follow-up was 4.6 years (interquartile range, 3.2–8.3).

**Table 1. Patient characteristics**

| Characteristic | N (%) or Median (IQR) | | |
|---|---|---|---|
| | All (n=76) | Received Bevacizumab >6 Weeks Before Surgery (n=53) | Received Bevacizumab ≤6 Weeks Before Surgery (n=23) |
| **Sex** | | | |
| Female | 50 (66%) | 35 (66%) | 15 (65%) |
| Male | 26 (34%) | 18 (34%) | 8 (35%) |
| **Median age, years (IQR)** | 65 (54–71) | 65 (55–71) | 66 (51–70) |
| **Diagnosis** | | | |
| Lung | 33 (43%) | 25 (47%) | 8 (35%) |
| Breast | 12 (16%) | 8 (15%) | 4 (17%) |
| Colorectal | 11 (14%) | 8 (15%) | 3 (13%) |
| Renal | 9 (12%) | 5 (9.4%) | 4 (17%) |
| Ovarian | 6 (7.9%) | 4 (7.5%) | 2 (8.7%) |
| Prostate | 1 (1.3%) | 1 (1.9%) | 0 (0%) |
| Other | 4 (5.3%) | 2 (3.8%) | 2 (8.7%) |
| **Metastatic disease** | 74 (97%) | 51 (96%) | 23 (100%) |
| **Radiation therapy** | 30 (39%) | 22 (42%) | 8 (35%) |
| **Fracture type** | | | |
| Impending | 21 (28%) | 15 (28%) | 6 (26%) |
| Nonpathologic | 15 (20%) | 10 (19%) | 5 (22%) |
| Pathologic | 40 (53%) | 28 (53%) | 12 (52%) |
| **Displaced fracture** | 49 (64%) | 33 (62%) | 16 (70%) |
| **Surgery type** | | | |
| Arthroplasty | 61 (80%) | 42 (79%) | 19 (83%) |
| Internal fixation | 15 (20%) | 11 (21%) | 4 (17%) |

IQR=interquartile range

Twenty-three patients (30%) were administered bevacizumab within six weeks of hip fracture surgery. Two patients in this group (8.7%) experienced complications: One developed deep vein thrombosis and the other experienced intraoperative fracture. None of the patients in this group developed wound complications or infections. Of the 53 patients (70%) who received bevacizumab outside of the perioperative window, five (9.4%) experienced complications. Two of these patients had wound drainage and three had deep vein thrombosis. No

patients in either group had wound dehiscence or required return to the operating room for complications associated with wound healing during the follow-up period. Of the 61 patients who underwent arthroplasty, four experienced complications; one of the four received bevacizumab within six weeks of surgery and three received bevacizumab prior to six weeks before surgery [Table 2].

**Table 2. Characteristics of patients who experienced a postoperative complication**

| Sex | Age | Diagnosis | Metastatic Disease | Radiation Therapy | Fracture Type | Displaced Fracture | Surgery Type | Months from Bevacizumab to Surgery | Days from Surgery to Complication | Type of Complication |
|---|---|---|---|---|---|---|---|---|---|---|
| **Perioperative bevacizumab (<6 weeks)** | | | | | | | | | | |
| Female | 51 | Lung | Yes | Yes | Pathologic | Yes | Arthroplasty | 0.36 | 29 | DVT |
| Male | 27 | Other | Yes | Yes | Pathologic | Yes | Internal fixation | 0.86 | 0 | Intraoperative fracture |
| **Bevacizumab outside perioperative window (>6 weeks)** | | | | | | | | | | |
| Female | 82 | Lung | Yes | No | Pathologic | Yes | Arthroplasty | 1.91 | 3 | DVT |
| Female | 64 | Lung | Yes | Yes | Pathologic | Yes | Internal fixation | 2.60 | 4 | Wound drainage |
| Female | 52 | Colorectal | Yes | Yes | Pathologic | Yes | Internal fixation | 15.43 | 6 | DVT |
| Male | 62 | Lung | Yes | Yes | Impending | No | Arthroplasty | 22.50 | 9 | DVT |
| Female | 73 | Lung | Yes | No | Impending | No | Arthroplasty | 31.84 | 4 | Wound drainage |

DVT, deep vein thrombosis

Univariable analyses did not indicate a significant difference in the complication rate between patients who received bevacizumab within the six-week perioperative window and those who received the drug prior to the window (HR, 0.92; 95% CI, 0.18–4.73; $P>0.9$).

## Discussion

Our study did not find the timing of bevacizumab administration before hip surgery to be associated with postoperative complications, including wound complications. Although many studies have investigated wound healing complications among bevacizumab recipients who underwent elective surgery, to our knowledge this study is the first to assess the relationship between preoperative bevacizumab use and postoperative wound complications among patients undergoing urgent orthopedic surgery for the hip. We selected patients requiring hip surgery for completed or impending fractures because these procedures are considered to be urgent, as delays may lead to complications related to immobility.

Bevacizumab's effectiveness in the management of various metastatic tumors stems from its inhibition of the neovascularization process. However, because neovascularization also plays an important role in wound healing, administrating bevacizumab has the potential to delay or disrupt wound healing.[14] Pharmacokinetic studies indicate that the drug has a relatively long half-life, which averages 21 days but can range from 10 to 50 days.[17] Although bevacizumab can remain in circulation for more than four half-lives (12 weeks), most studies have found that it is safe to perform surgery after six weeks from the last dose of this medication.[20,21]

Zhang et al. performed a systematic review and meta-analysis of randomized clinical trials to evaluate the risk of wound healing complications among patients receiving bevacizumab for various oncologic conditions. They found that the risk of wound healing complications was highest among patients with colon cancer, but no increase in risk was apparent among patients with gastroesophageal adenocarcinoma, metastatic renal cancer carcinoma, non–small cell lung cancer, or breast cancer.[22] Our study identified two patients with postsurgical wound dehiscence, both of whom had metastatic lung adenocarcinoma. None of the patients with metastatic colorectal cancer experienced wound complications in our series.

In an analysis of data from two clinical trials, Scappaticci et al. evaluated surgical wound complication rates in patients who underwent colorectal surgery while receiving bevacizumab. They reported that 10 of the 75 patients (13%) who had an urgent surgical procedure within 30 days of their last dose of bevacizumab and chemotherapy experienced wound healing complications, compared with 1 of the 29 patients (3%) who received chemotherapy alone. Although the difference was not statistically significant, the authors concluded that these findings could have clinical implications and warranted close observation of patients undergoing emergency surgery while receiving bevacizumab.[15] Our study found no cases of surgical wound complications among patients who underwent urgent hip fracture surgery within six weeks of receiving bevacizumab. Among patients who received bevacizumab more than six weeks prior to surgery, the wound complication rate was 3.8% (2/53). Of the two patients with wound healing complications who did not receive bevacizumab within the perioperative window, both

experienced wound drainage. These results suggest that the risk of surgical wound healing complications was not associated with the timing of bevacizumab administration relative to surgery in our study population.

In an analysis of retrospective data from three European hepatopancreatobiliary centers, Mahfud et al. investigated the impact of preoperative bevacizumab on postoperative complications following hepatectomy for colorectal liver metastasis. The authors found no differences in rates of severe complications, including wound healing complications, between 45 patients who received bevacizumab and chemotherapy within six weeks of surgery and a matched group of 45 patients who received chemotherapy alone. Moreover, a subgroup analysis found no differences in overall postoperative complications (including wound healing or thromboembolic complications) between the 20 patients who received bevacizumab less than six weeks prior to surgery and the 25 who received it more than six weeks prior to surgery.[23]

While many studies have not found an association between bevacizumab and wound healing, others have. For example, a retrospective study from the University of California, San Francisco, investigated the effect of bevacizumab on wound healing in patients who underwent second or third craniotomy for recurrent glioblastoma. One hundred sixty-eight patients did not receive bevacizumab, while 23 received it preoperatively and 18 postoperatively. The preoperative bevacizumab group had a significantly higher incidence of wound healing complications than the no-bevacizumab group (35% vs. 10%; P=0.004).[18,24,25]

Although the elevated risk of postoperative wound healing complications after administration of bevacizumab has been well documented, most studies have investigated the use of this medication among patients undergoing elective surgery, and have suggested that the medication not be administered until at least four weeks following surgery (if all wounds have fully healed).[14,22] However, the risks associated with bevacizumab in urgent surgical settings have not been thoroughly investigated.[15,23,26] Though more definitive evidence is needed, our study did not find a difference in postoperative wound healing complications between patients who received bevacizumab up to six weeks prior to surgery and those who received it more than six weeks prior to surgery. Nonetheless, given the theoretical risk, it is important to discuss the possibility of wound complications with patients who are receiving bevacizumab prior to hip surgery as a part of the informed consent process. Taking steps to optimize the patient's health, including providing a consultation with a nutritionist, may be helpful in reducing the risk of wound complications. The use of incisional negative-pressure wound dressing, which keeps the wound clean and dry, may also be useful for accelerating the healing process.[27] These approaches were used sporadically in our patients, but given the low rate of complications we could not assess their effect.

There are several limitations to this study. The most significant are the small sample size and low event rate, which together limit our ability to detect differences in the rate of complications. Because of the small sample size, it was not possible to adjust for important factors, such as surgery type or receipt of postoperative chemotherapy or radiotherapy. Still, our overall event rate (9.2%) is similar to that of other published series on the treatment of proximal femur metastases.[28] Because this study was retrospective, there may be confounding due to clinical differences that influenced the timing of bevacizumab administration and affected the complication rate. As a result, we emphasize that the results should be interpreted carefully, with emphasis on the uncertainty that remains regarding the definitive effect of preoperative bevacizumab on postoperative complications in this population; the 95% confidence interval for the effect of bevacizumab timing was 0.18 (protective effect of bevacizumab administered closer to surgery) to 4.73 (strong harmful effect of bevacizumab administered closer to surgery). Furthermore, the inclusion of patients who underwent two different types of surgery, one of which (arthroplasty) required a larger incision, may limit generalizability. Lastly, the patients in the study had different types of metastatic disease and hence received a variety of chemotherapy regimens, which may have affected wound healing outcomes.

## Conclusion

Bevacizumab has been associated with impaired wound healing, deep vein thrombosis, and hemorrhage, leading to recommendations that recipients not have surgery until at least six weeks after stopping this medication. While this recommendation can often be followed when patients are undergoing elective procedures, surgery for impending or completed hip fractures often cannot safely be delayed for weeks given the high rate of mortality associated with nonoperative management. This study found that the risk of complications was similarly low between patients treated with bevacizumab within the perioperative window and those treated outside the window, suggesting that urgent hip fracture surgery can be completed. Still, surgeons should discuss the risk of postoperative wound healing complications with the patient as part of informed consent.

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