Bevacizumab and Wound-Healing Complications: A Systematic Review

By

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Purpose

With current indications in breast, renal cell, brain, colorectal, and lung cancer, the anti-VEGF antibody bevacizumab (Avastin®) is increasingly utilized to treat various advanced-stage malignancies, reflecting the growing understanding of VEGF-mediated angiogenesis for tumor survival and growth. However, as VEGF also mediates normal physiological processes including the vasodilation, increased vascular permeability, and angiogenesis crucial for proper wound-healing, bevacizumab use in the perioperative setting can also be expected to lead to both undesirable wound-healing complications (WHCs) and their potentially-serious sequelae. Current recommendations aim to minimize bevacizumab-related WHCs by employing a very conservative interval between bevacizumab cessation and surgical intervention, but these are based primarily on provider judgment and not clinical evidence. Therefore, this paper systematically reviews the current clinical evidence concerning the probability, nature, and timing of bevacizumab-related WHCs, in hopes to modify and/or refine current management recommendations.

Introduction

Vascular endothelial growth factor (VEGF) is a family of glycoproteins that activate receptor tyrosine kinases on endothelial cells and circulating endothelial progenitor cells. While VEGF has been shown to recruit and differentiate progenitor cells from bone marrow, enhance vascular permeability, promote monocyte chemotaxis, and regulate immune response, its key clinically-relevant role is stimulation of angiogenesis.[1] Angiogenesis, the proliferation of blood vessels from pre-existing vasculature, is crucial for tumor survival and growth.[2] VEGF has been shown to stabilize and enhance abnormal tumor vasculature[3], while normal human vasculature remains largely independent of VEGF for survival.[4] Such selectivity renders inhibition of VEGF-mediated angiogenesis a highly appealing strategy in cancer treatment.
One such approach is bevacizumab (Avastin), an anti-VEGF monoclonal antibody that prevents downstream VEGF receptor activation in endothelial cells, causing anti-angiogenic inhibition of new tumor vasculature with normalization of existing tumor vasculature.[5, 6] These molecular effects have translated to improvements in clinical outcomes, as bevacizumab with chemotherapy improves response rates, progression-free survival, and overall survival in patients with various advanced-stage cancers over chemotherapy alone.[7] Currently, bevacizumab enjoys FDA indications for first or second-line treatment of metastatic colorectal cancer (mCRC) in combination with intravenous 5-fluorouracil (5-FU)-based chemotherapy, for first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC) in combination with paclitaxel and carboplatin chemotherapy, for second-line treatment of progressive disease glioblastoma multiforme (GBM) following prior single-agent therapy, and for metastatic renal cell carcinoma (RCC) in combination with interferon-alpha.[8]

On the basis that “the modest benefit observed in breast cancer trials to-date with the substantial adverse reactions observed in breast cancer trials fails to provide a favorable risk-benefit profile to support continued marketing of Avastin in a first-line metastatic breast cancer indication”[9], the FDA recently recommended withdrawing bevacizumab’s indication for metastatic HER2-negative breast cancer in combination with paclitaxel chemotherapy in patients who have not received prior chemotherapy. However, final decisions will be made pending a hearing with the manufacturer Genentech, so bevacizumab remains indicated for breast cancer at this time. Additional clinical trials are currently evaluating any therapeutic potential for treatment of endometrial, cervical, ovarian, gastric, prostate, and pancreatic cancers.[10-14]

The mammalian VEGF family consists of five glycoproteins: VEGFA, VEGFB, VEGFC, VEGFD, and PGF (placental growth factor). Of these, a specific 165-amino acid isoform of VEGFA is predominantly expressed in human solid cancers.[15] All bind to tyrosine kinase
receptors on target cells and initiate specific downstream signaling pathways.[16] VEGFR2, found exclusively on vasculature, mediates VEGF-induced angiogenesis. VEGFR1 is also found on vasculature and other cells but its function remains less elucidated. VEGFR3 preferentially binds VEGFC and VEGFD, is expressed on lymphatic endothelial cells, and mediates cardiovascular development and post-natal lymphangiogenesis.[15]

VEGF promotes tumor angiogenesis through several overlapping mechanisms: increased proliferation and survival of endothelial cells, increased migration and invasion of endothelial cells, increased permeability of pre-existing vasculature, and enhanced chemotaxis of bone marrow-derived endothelial progenitor cells.[15] Other non-vascular, pro-tumor VEGF effects include autocrine promotion of survival, migration, and invasion, suppression of host immune response, and aiding metastasis by targeting progenitor cells to destination organs.[17]

Bevacizumab is a humanized monoclonal antibody with a circulating half-life of ~20 days that neutralizes the activity of VEGF by selectively binding VEGF-A and inhibiting downstream activation of the VEGF2R receptor on endothelial cells.[5] Inhibition of VEGF activity may block tumor growth through several parallel and/or overlapping mechanisms. In addition to simply stopping further outgrowth of pre-existing vessels (so-called classical "sprouting angiogenesis"), VEGF inhibition may also vasoconstrict and normalize existing tumor vasculature, induce endothelial-cell apoptosis, sensitize tumor cells to concurrent chemotherapy, prevent recruitment of hematopoietic and endothelial progenitor cells, and directly impair tumor cell growth and metastasis.[15]

However, as VEGF also mediates many normal physiological processes, VEGF-targeted therapy can lead to multiple adverse reactions. For example, VEGF inhibition leads to decreased nitric oxide (NO) production in arteriolar walls resulting in vasoconstriction and consequently increased blood pressure[18], while proteinuria results from inhibition of VEGF-dependent interactions between podocytes and glomerular endothelial cells that disrupt the normal filtration barrier.[19] Although generally well-tolerated, bevacizumab therapy carries a
specific adverse reaction profile relating to inhibition of VEGF-mediated physiological processes. These toxicities include hypertension, proteinuria, gastrointestinal perforation, hemorrhage and other bleeding events, arterial thromboembolism, cardiac toxicity, leukoencephalopathy, rash, infusion-related hypersensitivity reactions, congestive heart failure, and hypothyroidism.[20-22] Literature regarding the pathophysiology, preclinical and clinical evidence, and optimal management recommendations for other bevacizumab-associated toxicities has been well-characterized elsewhere.[20-24]

Notably, angiogenesis is also crucial for proper wound repair[25], so bevacizumab also poses an increased risk of impaired wound healing[20], an important consideration in the perioperative care of patients receiving such therapy. Proper wound healing requires a highly structured and sequential series of events including phagocytosis, coagulation, chemotaxis, mitogenesis, and synthesis of collagen and other matrix components, and involves recruitment of various cell lineages including platelets, neutrophils, macrophages, lymphocytes, and fibroblasts, in that order.[26]

VEGF plays a role in many of these steps. First, after tissue injury, activated platelets release VEGF which helps recruit macrophages, fibroblasts, and endothelial cells. Second, monocytes also release VEGF which stimulates other monocytes to migrate into and remodel clots. Third, VEGF increases microvascular permeability which enhances both the early inflammatory response where recruited granulocytes clear bacteria and other wound debris and the late inflammatory response where recruited macrophages phagocytose debris and produce growth factors necessary for extracellular matrix production. Fourth, fibroblasts that deposit types I and III collagen to form new extracellular matrix also release VEGF.[26] Increased VEGF expression correlates with wound hypoxia and occurs as early as 3 days after wound induction before returning to normal levels by 3 weeks.[27]

Ultimately, VEGF mediates three effects for wound healing: vasodilation, increased vascular permeability, and angiogenesis. Potent vasodilation increases blood flow up to fivefold
and significantly aids oxygen and glucose delivery and waste removal.[26] Increased vascular permeability permits extravasation of fibrinogen, plasminogen, and other plasma proteins to help produce a pro-angiogenic extracellular matrix rich in fibrin and fibronectin, a substrate for further tissue regrowth.[26, 28] Angiogenesis occurs throughout these phases and remains crucial for proper wound healing.[25]

The above pathophysiological evidence suggests that bevacizumab therapy may increase the risk of undesirable wound-healing complications (WHCs). In fact, many of the clinical trials conducted to test the efficacy and effectiveness of bevacizumab in its various oncological indications have specifically reported wound-healing complications as part of bevacizumab’s toxicity profile. However, there remains no high-quality systematic review concerning the probability, timing, and nature of wound-healing complications resulting from bevacizumab use.

As bevacizumab therapy expands in clinical use in the oncological setting, and as many cancer patients undergo post-oncological aesthetic reconstruction, knowledge of its specific toxicity profile will become increasingly important, especially for the plastic surgeon who will increasingly be entrusted with proper wound care and elective reconstructions in these patients. As such, knowledge of the incidence, timing, and nature of bevacizumab-induced WHCs is increasingly critical to guide therapy and outline optimal evidence-based management recommendations. Therefore, this paper will systematically review the current clinical evidence to estimate the risk, timing, and nature of WHCs in patients who receive perioperative (neoadjuvant or adjuvant) bevacizumab.
Methods

The purpose of this paper is to systematically review the current clinical evidence to assess the probability, timing, and nature of wound-healing complications while receiving bevacizumab therapy in the oncological setting. Literature regarding the pathophysiology, preclinical and clinical evidence, and optimal management recommendations for other bevacizumab-associated toxicities has been well-characterized elsewhere[20-24]. The final work plans for this review were developed by the authors.

Data Sources and Searches

To identify relevant studies, we conducted a MEDLINE (1980 to June 11, 2011) search using the MESH headings “bevacizumab”, “avastin”, “mechanism”, “complication”, “wound”, “surgery”, “colorectal”, “breast”, “renal cell”, “brain”, “lung”, and “cancer.” Each search was limited to studies and trials performed in humans, as preclinical and pathophysiological evidence was excluded. Furthermore, studies were limited to those published in the English language. We also hand searched the bibliographies of included articles, searched our own files, and queried content experts at our institution to identify additional possibly-relevant studies as well. In addition, we also performed related articles searches of all included MEDLINE articles.

Study Selection

We included studies of any design that were conducted in academic institutions and have been necessarily approved by the Institutional Review Board (IRB). Studies had to specify an intervention of FDA-approved bevacizumab therapy given to a patient with an oncological diagnosis. Neoadjuvant bevacizumab had to be given at most 60 days (~8 weeks) before surgical intervention, while adjuvant bevacizumab had to be given at most 60 days (~8 weeks) after. Studies had to specifically report a wound-healing complication rate that specified the
nature and timing of WHCs, although this did not have to be the study’s primary outcome of interest. Furthermore, studies had to report a follow-up period of at least one year, with wound-healing complications occurring one year after cessation of bevacizumab therapy not considered a bevacizumab-related WHC. The primary outcome of interest for this study was the incidence of WHC, with timing and nature being secondary outcomes of interest.

Table 1. PICOTTS Eligibility Criteria for Studies Included In Review.

<table>
<thead>
<tr>
<th></th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with oncological diagnoses receiving bevacizumab for an FDA-approved indication</td>
<td>Patients with oncological diagnoses receiving bevacizumab as off-label use not currently approved by the FDA, or patients without oncological diagnoses</td>
</tr>
<tr>
<td>Intervention</td>
<td>Bevacizumab therapy occurring around or during surgical intervention, with or without concurrent chemotherapy</td>
<td>Bevacizumab therapy with or without concurrent chemotherapy occurring without any reported surgical intervention</td>
</tr>
<tr>
<td>Control</td>
<td>Chemotherapy with surgical intervention, but control group not necessary</td>
<td>Chemotherapy without surgical intervention</td>
</tr>
<tr>
<td>Outcome</td>
<td>Clinical outcome where the incidence, timing, and nature of predefined wound-healing complications specifically reported; did not have to be primary outcome of study</td>
<td>Wound-healing complications not specifically defined, timing and nature not provided, any intermediate outcomes</td>
</tr>
<tr>
<td>Time (intervention)</td>
<td>Neoadjuvant bevacizumab given at most 60 days (~8 weeks) before surgery and/or adjuvant bevacizumab given at most 60 days (~8 weeks) after surgery</td>
<td>Neoadjuvant bevacizumab given more than 60 days (~8 weeks) before surgery and/or adjuvant bevacizumab given more than 60 days (~8 weeks) after surgery</td>
</tr>
<tr>
<td>Time (follow-up)</td>
<td>Patient follow-up of at least one year after cessation of bevacizumab therapy, with any reported WHCs occurring one year after bevacizumab cessation discounted</td>
<td>Patient follow-up less than one year after cessation of bevacizumab therapy</td>
</tr>
<tr>
<td>Study Design</td>
<td>Randomized-controlled trials, cohort studies, case control, or case series of at least 40 patients</td>
<td>Single case report, any study with less than 40 patients</td>
</tr>
</tbody>
</table>
We excluded studies that did not clearly define what was considered a wound-healing complication, contained less than 40 patients, received neoadjuvant bevacizumab more than 60 days before surgery and/or adjuvant bevacizumab more than 28 days after surgery, did not report the timing of wound-healing complications, did not have a quantitative study design, did not include some type of surgical intervention, applied bevacizumab therapy as off-label use and/or in patients without oncological diagnoses, did not have at least a one-year median follow-up period, or were perceived to be very poor quality upon initial examination.

**Study Type**

The following study types were considered acceptable for inclusion: case series, case-control analyses, cohort studies, randomized-controlled trials. The following study types were not considered acceptable and excluded: single case report, expert opinion.

**Data Extraction**

Both authors independently reviewed titles, abstracts, and full articles (if necessary) to determine inclusion eligibility, with disagreements resolved by discussion. The first author abstracted study information into tables, with both checking information for accuracy. Both authors independently assessed study quality and then compared results, with disagreements resolved by discussion as well.

**Quality Assessment**

Quality was graded using criteria adapted from the United States Preventive Services Task Force (USPSTF) which had been used in numerous previous reviews. For each study, reviewers graded pre-specified criterion as good (G), fair (F), or poor (P). Ratings for each time were converted into numerical values as follows: good = 2, fair = 1, and poor = 0. Then, a composite score consisting of the average of these ratings was calculated and reported for each
study, with each item weighted equally. The final quality of the study was determined by the composite score, with 1.5 or higher considered good (G), 1.0 to 1.49 considered fair (F), and less than 1.0 considered poor (P).

**Measurement Assessment**

To be included in this review, studies had to specifically define what criteria was used to define all wound-healing complications. Such criteria had to be constructed before implementation of the study, had to be consistently applied to all study patients, and had to consist of clinically-documented events determined to be WHCs by providers. WHC criteria did not necessarily have to include severity of each complication. The bevacizumab dose had to be specifically reported and had to be consistent with FDA-approved dosing by indication.

**Data Synthesis and Analysis**

After data abstraction and quality assessment, this study’s authors met for discussion about result, comparing and contrasting relevant features of studies, prioritizing certain study sizes and designs, and continuing iterative review until reaching consensus about key message and conclusions. No meta-analyses could be performed to the heterogeneity of study populations, oncological diagnoses, timing and duration of bevacizumab therapy, and wound-healing complication definitions.
Results

Search Results

Overall, we identified eight articles that were reviewed in final analysis and included in our review; all eight were identified through primary literature search and none through hand review or expert inquiry (Figure 1).

Figure 1. Flowchart for Study Inclusion Process.
Study Design

A summary of included studies is provided in Table 2. One (Allegra et al. [29]) was a high-powered prospective randomized controlled trial. Two (Kozloff et al. [30], Jonasch et al. [31]) were prospective cohort analyses, one (Gruenberger et al. [32]) was a prospective case series, one (Scappaticci et al. [33]) was a retrospective case-control study, and another three (Kesmodel et al. [34], Clark et al. [35], Golshan et al. [36]) were retrospective case series.

Table 2. Summary of Included Articles.

<table>
<thead>
<tr>
<th>Source</th>
<th>Indication</th>
<th>Design</th>
<th>Quality Grade</th>
<th>Sample Size</th>
<th>Therapy Timing</th>
<th>Interval</th>
<th>WHC Definition</th>
<th>WHC rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gruenberger, et al. 2008</td>
<td>mCRC</td>
<td>Case series</td>
<td>1.2 (F)</td>
<td>56</td>
<td>Neoadjuvant + adjuvant</td>
<td>35 d, 35 d</td>
<td>CTCAEv3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0%</td>
</tr>
<tr>
<td>Kesmodel, et al. 2008</td>
<td>mCRC</td>
<td>Case control</td>
<td>1.4 (F)</td>
<td>81</td>
<td>Neoadjuvant</td>
<td>49 d</td>
<td>Infection or collection that required partial wound opening and local wound care, wound complication requiring surgery, other</td>
<td>28%</td>
</tr>
<tr>
<td>Kozloff, et al. 2009</td>
<td>mCRC</td>
<td>Cohort</td>
<td>1.4 (F)</td>
<td>521</td>
<td>Neoadjuvant</td>
<td>≤ 60 d</td>
<td>Wound dehiscence, wound infection, wound bleeding, other wound complications</td>
<td>4.4%</td>
</tr>
<tr>
<td>Scappaticci, et al. 2005</td>
<td>mCRC</td>
<td>Case control</td>
<td>1.8 (G)</td>
<td>75</td>
<td>Neoadjuvant Adjuvant</td>
<td>≤ 60 d</td>
<td>Abnormal or delayed healing, wound dehiscence, bowel perforation, fistula, abscess, hemorrhage</td>
<td>13% 1.3%</td>
</tr>
<tr>
<td>Allegra et al. 2009</td>
<td>mCRC</td>
<td>RCT</td>
<td>1.8 (G)</td>
<td>1,326</td>
<td>Adjuvant</td>
<td>46 d</td>
<td>CTCAEv3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.7%</td>
</tr>
<tr>
<td>Clark et al., 2010</td>
<td>GBM</td>
<td>Case series</td>
<td>0.6 (P)</td>
<td>41</td>
<td>Neoadjuvant + adjuvant</td>
<td>36 d</td>
<td>Infection, dehiscence, CSF leakage, pseudomeningocele, osteomyelitis</td>
<td>22%</td>
</tr>
<tr>
<td>Golshan et al., 2011</td>
<td>Breast</td>
<td>Case series</td>
<td>0.8 (P)</td>
<td>51</td>
<td>Neoadjuvant + adjuvant</td>
<td>42 d, 21 d</td>
<td>Seroma, abscess, hematoma, native flap necrosis, reconstruction flap necrosis, cellulitis requiring antibiotics</td>
<td>43%</td>
</tr>
<tr>
<td>Jonasch et al., 2009</td>
<td>RCC</td>
<td>Cohort</td>
<td>1.0 (F)</td>
<td>50</td>
<td>Neoadjuvant</td>
<td>28 d</td>
<td>Wound dehiscence, delayed wound healing</td>
<td>24%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Indication: mCRC = metastatic colorectal cancer, GBM = glioblastoma multiforme, RCC = renal cell carcinoma

<sup>2</sup> As described in the “Data Extraction and Quality Assessment” subsection of “Methods”, each study’s quality was graded according to a composite score that ranked each component as good (G), fair (F), or poor (P)

<sup>3</sup> National Cancer Institute’s 2003 Common Terminology Criteria for Adverse Events version 3.0[37]
Study and Source Populations and Measurement Outcomes

Included studies spanned four of bevacizumab’s five current oncological indications: metastatic colorectal cancer (Gruenberger et al., Kozloff et al., Kesmodel et al., Scappaticci et al., Allegra et al.), glioblastoma multiforme (Clark et al.), renal cell carcinoma (Jonasch et al.), and breast cancer (Golshan et al.). Notably, no studies met the inclusion and exclusion criteria for the remaining indication of non-small cell lung cancer. In addition, the timing of bevacizumab therapy ranged from exclusively neoadjuvant (Kozloff et al., Kesmodel et al., Scappaticci et al., Jonasch et al.) to exclusively adjuvant (Allegra et al.) to combined neoadjuvant and adjuvant regimens (Gruenberger et al., Clark et al., Golshan et al.). The duration of the bevacizumab-surgery interval ranged from 28-60 days in the neoadjuvant setting to 21-36 days in the adjuvant setting.

Three included studies (Gruenberger et al., Allegra et al., Jonasch et al.) were trials evaluating the efficacy of novel bevacizumab-containing chemotherapy regimens and therefore had primary efficacy outcomes of all-cause mortality or progression-free survival, though specific wound-healing complications were reported as part of an overall safety and toxicity profile. The remaining five studies (Kesmodel et al., Kozloff et al., Scappaticci et al., Clark et al., Golshan et al.) were constructed to specifically examine the incidence of bevacizumab-related wound-healing complications and thus had primary safety outcomes of postoperative wound-healing complication incidence.

Critical Appraisal of Included Studies

Tables 3a and 3b provide a summary of critical appraisal of the eight included studies; justification for overall study quality rating can be found here.
Table 3a. Critical Appraisal of Included Studies.

<table>
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<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Prospective, single-center, nonrandomized phase II clinical trial (case series) evaluating efficacy and toxicity of bevacizumab with capecitabine and oxaliplatin as neoadjuvant therapy for metastatic colorectal cancer</td>
<td>Retrospective case-control analysis evaluating postoperative complication rate after neoadjuvant bevacizumab vs. chemotherapy and mCRC hepatectomy</td>
<td>Prospective, multi-center cohort study to elucidate safety and effectiveness of bevacizumab-containing chemotherapy for mCRC</td>
<td>Prospective, phase III RCT to evaluate the safety and effectiveness of adjuvant bevacizumab with FOLFOX chemotherapy for stage II and III CRC.</td>
</tr>
<tr>
<td><strong>Source population</strong></td>
<td>Patients from Europe and United States with surgically resectable stage IV colorectal cancer metastasized to liver</td>
<td>Patients from the United States with isolated hepatic metastases from colorectal cancer</td>
<td>United States patients with previously untreated mCRC</td>
<td>United States patients with stage II and III colorectal cancer</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>56 patients with histologically-confirmed resectable mCRC hepatic metastases at high risk for early recurrence, with ECOG performance status 0-1 and adequate bone marrow reserve and renal and hepatic function. Exclusion criteria: prior chemotherapy, prior coagulopathy, CNS metastases, significant CV disease</td>
<td>125 patients who received neoadjuvant chemotherapy (44 chemo only, 81 with bevacizumab) at a median of 58 days prior to hepatic mCRC resection. Study did not report specific exclusion criteria, other than assumed surgical resectability</td>
<td>1,953 patients with locally advanced or metastatic CRC previously untreated receiving a bevacizumab-containing chemotherapy regimen, of which 521 subsequently underwent surgical resection within 60 days. No exclusion criteria specified</td>
<td>2,710 patients with stage II or III CRC randomized to receive adjuvant FOLFOX (1,356) or adjuvant FOLFOX + bevacizumab (1,354) after undergoing surgical resection. Exclusion criteria: history of stroke, TIA, vascular disease, arterial thrombosis (MI).</td>
</tr>
<tr>
<td><strong>Initial comparability of groups</strong></td>
<td>Not applicable, as no control group</td>
<td>Comparable, as did not differ by age, stage, comorbidity, BMI, tumor size, or procedural variables. Bevacizumab group did have more metastatic liver lesions (p = 0.04).</td>
<td>Not applicable, as no control group</td>
<td>Comparable, as did not differ by age, gender, stage, and race. Study did not report patient comorbidity and procedural variables, but randomized so should be similar too</td>
</tr>
<tr>
<td><strong>Drop-outs, adherence, cross-overs</strong></td>
<td>Study did not report any drop-outs or adherence issues; cross-overs not applicable</td>
<td>Study did not report drop-outs, cross-overs, or adherence issues</td>
<td>Of the initial 1,953, 83 (4%) dropped out, 150 (8%) were lost to follow-up, and 88 (4%) withdrew</td>
<td>Of the 1,354 assigned to bevacizumab, 22 (1.6%) dropped out. No cross-overs</td>
</tr>
<tr>
<td><strong>Selection bias</strong></td>
<td>Intermediate potential (fair), as only 56 subjects were enrolled and assessed as “surgically resectable” and “high risk of recurrence” according to clinical judgment</td>
<td>Intermediate potential (fair), as subjects were initially enrolled into groups according before study by varying criteria over time</td>
<td>Low potential (good). To reduce selection bias, sites were instructed to recruit all eligible patients, but no non-enrolled patient log was kept</td>
<td>Low potential (good), as both arms were randomized after stratifying by number of positive lymph nodes</td>
</tr>
<tr>
<td><strong>Outcome measurement</strong></td>
<td>WHCs graded via CTCAEv3.0</td>
<td>Wound infection or collection requiring surgery, other</td>
<td>Wound dehiscence, infection, bleeding, and other wound complications</td>
<td>WHCs graded via CTCAEv3.0</td>
</tr>
<tr>
<td><strong>Measurement bias</strong></td>
<td>Low potential (good), as CTCAEv3.0 provides a systematic and consistent independent guideline to evaluate specific toxicities in oncological patients, thus</td>
<td>Intermediate potential (fair), as WHCs not clearly or systematically defined by independent system,</td>
<td>Low potential (good). Though WHCs not independently set, high sample size would neutralize random biases from</td>
<td>Low potential (good), as CTCAEv3.0 provides a systematic, independent guideline to evaluate</td>
</tr>
<tr>
<td>Confounders</td>
<td>Confounding potential</td>
<td>Analysis</td>
<td>Results</td>
<td>Clinical importance</td>
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<td>-------------</td>
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<tr>
<td>Age, tumor stage, patient comorbidity that could independently affect wound-healing (obesity, diabetes, nutrition status)</td>
<td>High potential (poor), as study was single-arm of 56 patients and patient comorbid conditions were not reported or controlled</td>
<td>Efficacy (tumor response) and safety (rate of grade 3/4 adverse events)</td>
<td>0% rate of grade 3/4 wound-healing complications</td>
<td>Significant, as bevacizumab expands in use as perioperative therapy for oncological patients who undergo surgical resection</td>
</tr>
<tr>
<td>Age, tumor stage, comorbidity (diabetes, CV disease), BMI, procedural variables (duration, EBL, type)</td>
<td>Low potential (good), as two groups were similar and most known confounders reported and controlled for</td>
<td>Incidence of post-operative wound-healing complication</td>
<td>25% chemo vs. 28% bevacizumab, p = 0.68</td>
<td>Significant, as bevacizumab is increasingly used as neoadjuvant therapy for hepatic mCRC</td>
</tr>
<tr>
<td>Age, tumor stage, tumor size and site, comorbidity (diabetes, PAD, BMI), procedural variables</td>
<td>Low potential (good), as most known confounders were reported and controlled for in multivariate analysis</td>
<td>WHC incidence in subgroup of patients undergoing surgery</td>
<td>23/521 (4.4%, 95% CI 2.7-6.2%) WHC rate</td>
<td>Significant, as bevacizumab is increasingly used as neoadjuvant therapy for hepatic mCRC</td>
</tr>
<tr>
<td>Age, stage, tumor size and site, comorbidity (BMI, diabetes, nutrition status), procedural variables</td>
<td>Low potential (good), as study was large and randomized, so confounders controlled for even if not reported</td>
<td>Effectiveness (PFS) and safety (rate of grade 3/4 toxicities)</td>
<td>1.7% bevacizumab vs. 0.3% FOLFOX only, p &lt; 0.01</td>
<td>Significant, as bevacizumab is increasingly used in adjuvant setting for CRC, even if not metastatic</td>
</tr>
</tbody>
</table>

¶ Graded as good (2), fair (1), or poor (0), with a composite average then recorded as study’s overall quality
Table 3b. Critical Appraisal of Included Studies (continued).

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Design</th>
<th>Source Population</th>
<th>Initial comparability of groups</th>
<th>Drop-outs, adherence, cross-overs</th>
<th>Selection bias</th>
<th>Outcome measurement</th>
<th>Measurement bias</th>
<th>Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States patients with previously untreated mCRC considered surgically resectable</td>
<td>Retrospective, case-control analysis to assess postoperative WHC rate after neoadjuvant bevacizumab from two randomized studies in mCRC patients</td>
<td>United States patients with surgically-resectable mCRC</td>
<td>Comparable, as the two groups (chemotherapy alone, chemotherapy + bevacizumab) were pooled from two other randomized studies</td>
<td>Study did not report drop-outs, cross-overs, or adherence issues</td>
<td>Low potential (good), as study pooled data from two other randomized studies, using computers, which minimizes selection bias.</td>
<td>WHCs graded via CTCAEv3.0</td>
<td>Low potential (good), as CTCAEv3.0 provides a consistent, systematic and independent guideline, thus equal, valid, and reliable</td>
<td>Age, tumor stage, tumor size and site, comorbidity</td>
</tr>
<tr>
<td>1,132 previously-untreated mCRC patients: 516 got chemotherapy alone, 616 bevacizumab of which 305 received resection (230 neoadjuvant, 75 adjuvant). Exclusion criteria: major surgery up to 28 days before, vascular disease and/or coagulopathy</td>
<td>Retrospective single-center case-series to assess wound healing complication risk of second or third craniotomies for recurrent GBM</td>
<td>United States patients with triple-negative resectable breast cancer</td>
<td>Not applicable, as no control group</td>
<td>No dropouts, cross-overs, or adherence issues reported</td>
<td>High potential (poor), as no consistent criteria defined or reported for why study patients got bevacizumab in addition to standard chemoradiation before or after recurrent GBM resection</td>
<td>Surgical site infection, wound dehiscence, CSF leakage, pseudomeningocele, bone flap osteomyelitis</td>
<td>Low potential (good), as single reviewer used same specifically-defined WHC criteria for all cases, thus equal, valid, and reliable</td>
<td>Age, tumor stage, tumor size and site, comorbidity</td>
</tr>
<tr>
<td>Retrospective single-center trial to assess surgical morbidity of neoadjuvant bevacizumab for triple-negative breast cancer</td>
<td>United States patients with triple-negative resectable breast cancer</td>
<td>Groups did not differ by age, mean tumor size, or resection type (BCT vs. mastectomy), but differed by stage</td>
<td>Not applicable, as single-arm and no control group</td>
<td>Of 52, 2 (4%) dropped out and 8 (16%) lost to f/u</td>
<td>Intermediate potential (fair). Both arms had similar inclusion criteria that was clearly specified, though selection into bevacizumab arm or not was offered by clinician without oversight</td>
<td>Seroma, abscess, hematoma, native flap necrosis, reconstruction flap necrosis, cellulitis requiring antibiotics</td>
<td>Intermediate potential (fair). Prespecified and clear inclusion criteria, but whether or not bevacizumab was offered depended on clinical judgment</td>
<td>Age, tumor stage, tumor size and site, comorbidity</td>
</tr>
<tr>
<td>Prospective non-comparative phase II (cohort) trial evaluating efficacy and safety of neoadjuvant bevacizumab in RCC</td>
<td>United States patients with surgically-resectable RCC</td>
<td>No dropouts, cross-overs, or adherence issues reported</td>
<td>Not applicable, as single-arm and no control group</td>
<td>Of 52, 2 (4%) dropped out and 8 (16%) lost to f/u</td>
<td>Intermediate potential (fair). WHC criteria were vague, especially “delayed wound healing”, so not very equal, valid, and/or reliable</td>
<td>Wound dehiscence, delayed wound healing</td>
<td>High potential (poor). WHC criteria were vague, especially “delayed wound healing”, so not very equal, valid, and/or reliable</td>
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<td>Age, tumor stage, tumor size and site, comorbidity</td>
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</tbody>
</table>
| Confounding potential | Location, patient comorbidity (BMI, diabetes, nutrition status, CV disease), prior treatment (chemoradiation), procedural variables | Patient comorbidity (BMI, diabetes, nutrition status, CV disease), prior radiation therapy, procedural variables | Size, patient comorbidity (BMI, diabetes, nutrition status, CV disease), prior radiation therapy, procedural data (length, etc…)

| Confounding potential | Low potential (good), as data was pooled from two other randomized studies which minimizes confounding. | High potential (poor), as possible confounders not reported or controlled for in analysis | High potential (poor). Study did not report or control for most likely confounders in analysis, simply reporting crude rate

| Analysis | Postoperative WHC incidence | Postoperative WHC incidence | Postoperative WHC incidence

| Results | 3/230 (1.3%, 95% CI 0.3-3.8%) adjuvant; 10/75 (13%, 95% CI 7-23%) neoadjuvant | Overall 9/41 (21.9%) Neoadjuvant 8/23 (34.8%), adjuvant 1/18 (5.6%) | 11/28 (39%) cisplatin vs. 22/41 (43%) in bevacizumab, p = 0.82 12/50 (24%) WHC rate after neoadjuvant bevacizumab

| Clinical importance | Significant, as bevacizumab is used as adjuvant and neoadjuvant therapy for hepatic mCRC | Significant, as bevacizumab is indicated for recurrent GBM now | Significant, as bevacizumab is used for neoadjuvant therapy, and many breast cancer patients undergo immediate reconstruction 12/50 (24%) WHC rate after neoadjuvant bevacizumab

| Internal validity | Good. Strict inclusion and exclusion criteria | Fair. Results applicable to study population | Good. Strict inclusion and exclusion criteria

| External validity | Fair. Strict inclusion and exclusion criteria from randomized studies but no selection bias means study population approximates source population fairly | Poor. Study did not specify inclusion or exclusion criteria or indicate why patients got bevacizumab for recurrent GBM over just chemoradiation, so less applicable to overall source population of recurrent GBM patients | Good. Study population approximates source population well, as exclusion criteria did not leave out most patients in the U.S. with RCC

| Comments | Although retrospective, this study pooled data from two randomized and high-powered studies, with little measurement bias, and thus well evaluates WHC incidence in the neoadjuvant and adjuvant setting | Retrospective and small study which didn’t report and control for numerous confounders, high selection bias potential, and limited external validity, these findings are uncertain | Retrospective and small, this study didn’t control for most variables that could confound impaired wound-healing, making results very uncertain

¶ Graded as good, fair, or poor, with a composite average then recorded as study’s overall quality
Measurement Bias Potential

All studies explicitly defined what they considered a wound-healing complication, but this definition was not necessarily consistent from one study to the next, as evidenced in Table 2. Inconsistency and inherent subjectivity in WHC definition rendered each of the studies to be at risk for measurement bias.

Several considerations were consistent across all studies and could have led to possible measurement bias. First, none of the eight studies included any type of blinding when measurements were being recorded, as providers were always aware of which patients were on bevacizumab therapy. This introduces some potential measurement bias in all eight studies. However, blinding may not be feasible, as wound-healing complications are recorded by the same surgical oncologists who provide appropriate follow-up after surgical intervention, and therefore must be aware if the patient received neoadjuvant or adjuvant bevacizumab. Nonetheless, this consideration should be taken into account when assessing measurement bias.

Second, the dose of bevacizumab did vary between studies but was consistent with FDA-approved dosing. For GBM, Clark et al. used 10 mg/kg. For breast cancer, Golshan et al. used 15 mg/kg. For mCRC, Gruenberger et al., Kozloff et al., Kesmodel et al., Allegra et al., and Scappaticci et al. all used 5 mg/kg. Finally, for RCC, Jonasch et al. provided 10 mg/kg. The variations in dosing introduce possible measurement bias as higher bevacizumab doses may lead to higher reported WHCs.

Five of the eight studies had little potential for measurement bias. Gruenberger et al., Scappaticci et al., and Allegra et al. utilized the increasingly-favored CTCAEv3.0[37], which provides systematic, consistent, and independently-determined guidelines to evaluate and grade adverse reactions in oncological settings, including wound-healing. This makes measuring WHCs equal, valid, and reliable, and thereby minimizes measurement bias. On the other hand, Clark et al.’s differing WHC criteria included CSF leakage, pseudomeningocele
formation, and osteomyelitis, as the location of the craniotomy incision in the scalp for GBM warrants these specific considerations as possible sequelae secondary to impaired wound-healing. Since a single author reviewed all cases retrospectively in this study with a predetermined and specific set of criteria, measurement bias potential was minimized here too. Finally, although Kozloff et al. used a broader WHC definition that included dehiscence, infection, bleeding, and “other”, the large sample size (n = 521) means random biases from clinical judgment are more likely to be neutralized.

Two of the eight studies had intermediate potential for measurement bias. Kesmodel et al. defined WHCs as any “infection or collection requiring wound opening and local wound care or wound complication requiring surgery.” The stipulation that the complication would require subsequent surgical intervention represents an objective measure that somewhat offsets the broader and vaguer WHC criteria here. Golshan et al. defined a WHC to include seroma, abscess, hematoma, native or reconstruction flap necrosis, and cellulitis requiring antibiotic therapy. Including flap necrosis here is justified as many breast cancer patients undergo reconstruction following mastectomy. However, these umbrella criteria are broader than what is typically considered a wound-healing issue, such as abscess or cellulitis which may be unrelated.

The remaining study, Jonasch et al., had a high potential for measurement bias as WHCs were defined as either wound dehiscence or “delayed wound healing”; the latter requirement is vague, qualitative, and easily variable depending on clinical judgment.

Three of the studies (Gruenberger et al., Scappaticci et al., Allegra et al.) included a grading system with also ranked the severity of the reported WHC. Another two (Kesmodel et al., Golshan et al.) included stipulations in their WHC criteria such that only severe complications would be reported: Kesmodel et al. required surgical re-intervention, and Golshan et al. included only more serious complications. The remaining three (Jonasch et al., Clark et al., Kozloff et al.) did not include any schema which would separate severe WHCs from less-
severe ones. In the lattermost group, the lack of differentiation by WHC-severity introduces bias as less-severe WHCs (such as healing delayed by one week) are weighted as equally as more-severe WHCs (such as meningitis or osteomyelitis).

Confounding Potential

Many patient and procedural factors could independently and differentially affect the postoperative wound-healing status in these studies, other than the presence of bevacizumab therapy. Known confounders can be classified into patient variables, tumor variables, and procedural variables (Table 4). Potential patient confounders include age, gender, diabetes, hypertension, nutritional status, cardiovascular disease, peripheral arterial disease, liver disease, acute or chronic renal disease, and prior radiation therapy. Potential tumor confounders include type, stage, size and location of primary, and ease of resectability. Potential procedural confounders include type, duration of surgery, estimated-blood loss, location and size of incision, nature of concurrent chemotherapy, and duration between bevacizumab cessation and surgical intervention.

Table 4. Potential Wound-Healing Confounders

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Type</td>
<td>Type</td>
</tr>
<tr>
<td>Gender</td>
<td>Stage</td>
<td>Duration</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Size</td>
<td>Incision Location and Size</td>
</tr>
<tr>
<td>Nutritional Status</td>
<td>Location of Primary</td>
<td>Estimated Blood Loss</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Ease of Resectability</td>
<td>Concurrent Chemotherapy</td>
</tr>
<tr>
<td>Peripheral Arterial Disease</td>
<td></td>
<td>Bevacizumab-Surgery Duration</td>
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<td>Liver Dysfunction</td>
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<td>Renal Disease</td>
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<td>Prior Radiation Therapy</td>
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</table>

The ability of each study to address potential confounders primarily determined the certainty of its results. Four of the eight studies were considered to have minimal potential for confounding. Kesmodel et al.’s retrospective analysis compared cases of neoadjuvant
bevacizumab with chemotherapy against controls of neoadjuvant chemotherapy only before hepatic metastectomy. The two groups did not differ by age, stage, numerous comorbidities (cardiovascular disease, hypertension, pulmonary disease, renal disease, hepatobiliary disease, diabetes, BMI), and numerous procedural variables (procedure type, number and nature of neoadjuvant chemotherapy regimens, bevacizumab-surgery duration), although the bevacizumab cases did have a higher number of metastatic liver lesions (p = 0.04). Since the two groups did not differ significantly by numerous confounders that were properly reported, the final results are more trustworthy. Kozloff et al.’s cohort study also reported numerous potential confounders: age, race, gender, primary tumor site, mean preoperative albumin, proportion and type of prior adjuvant therapy, site of metastatic disease, diabetes, hypertension, arterial disease, anticoagulation therapy use, and bevacizumab-surgery duration. Many of these were controlled for via multivariate Poisson regression analysis, and thus adequate reporting with statistical normalization minimizes confounding here too. The other two studies (Allegra et al. and Scappaticci et al.) were randomized and high-powered, such that even though not all known specific confounders were reported, confounding was minimized if not eliminated.

The remaining four studies were all rated as having high potential for confounding. Gruenberger et al. reported only basic patient information (age, gender, primary tumor site, hepatic metastases distribution) and ignored other potential confounders including patient comorbidity and procedural variables. Similarly, Golshan et al. reported only basic patient information, ignored most tumor and procedure confounders, and did not compare the two groups in a formal, statistical manner. In addition, Clark et al.’s also did not report most patient, tumor, and procedural confounders, and neither did Jonasch et al. In all four studies, the final bevacizumab-related WHC incidence is very uncertain, as it remains difficult to attribute the recorded WHC incidence to bevacizumab therapy as opposed to the numerous potential patient, tumor, and/or procedural confounders.
**Overall Study Quality**

Overall study quality broke down as follows. Two studies were ultimately categorized as “Good” quality: Scappaticci *et al.*’s case-control analysis of neoadjuvant bevacizumab before hepatic resection of metastatic colorectal cancer and Allegra *et al.*’s randomized-controlled trial of adjuvant bevacizumab after primary resection of stage II and III colorectal cancer. Four studies were ultimately categorized as “Fair” quality: Gruenberger *et al.*’s case series of neoadjuvant and adjuvant bevacizumab before and after hepatic resection of metastatic colorectal cancer, Kesmodel *et al.*’s case-control analysis of neoadjuvant bevacizumab before hepatic resection of metastatic colorectal cancer, Kozloff *et al.*’s cohort study of neoadjuvant bevacizumab before hepatic resection of metastatic colorectal cancer, and Jonasch *et al.*’s cohort study of neoadjuvant bevacizumab before cytoreductive nephrectomy for renal cell carcinoma. Finally, the remaining two studies were classified as “Poor” quality: Clark *et al.*’s case series of neoadjuvant and adjuvant bevacizumab before and after repeat craniotomy for recurrent glioblastoma multiforme, and Golshan *et al.*’s case series of neoadjuvant and adjuvant bevacizumab before and after surgical resection for triple-negative breast cancer.

**The Effect of Bevacizumab Therapy on Wound-Healing**

The results of the “Good” studies can be concluded with the most certainty. Scappaticci *et al.* observed a 1.3% (95% CI: 0.3-3.8%) WHC rate in the adjuvant setting and a 13% (95% CI: 7-23%) in the neoadjuvant setting. Allegra *et al.* observed a 1.7% WHC rate with adjuvant bevacizumab, as opposed to 0.3% with adjuvant chemotherapy alone (p = 0.01). Importantly, both studies applied the same CTCAEv3.0 criteria to define wound-healing complications. Both yielded a WHC rate in the adjuvant bevacizumab setting that was similar and low, at ~2%. In addition, Scappaticci *et al.* supports the notion that neoadjuvant bevacizumab raises the WHC risk more than adjuvant bevacizumab (13% versus 1.3%), while Allegra *et al.* suggests that
adjuvant bevacizumab raises the WHC risk more than adjuvant chemotherapy alone (1.7% versus 0.3%).

The results from the “Fair” studies should be interpreted with more caution, though not discounted altogether. Gruenberger et al. found a 0% WHC rate amongst 56 mCRC patients, though only severe grade 3 and 4 complications were recorded, so less-severe WHCs may have occurred but not been considered. Kesmodel et al. reported a 28% WHC rate following neoadjuvant bevacizumab that did not differ significantly (p = 0.68) from the 25% WHC rate following neoadjuvant chemotherapy alone. This finding disagrees with Allegra et al. which implied a higher WHC risk than chemotherapy alone, though Kesmodel et al. occurred in the neoadjuvant setting and Allegra et al. in the adjuvant. Kozloff et al. reported a 4.4% (95% CI: 2.7-6.2%) WHC rate after neoadjuvant bevacizumab. This is significantly smaller than Scappaticci et al.’s 13% rate, though the difference here can be attributed (at least partially) to differing WHC criteria. Jonasch et al. observed a 24% WHC rate after neoadjuvant bevacizumab, significantly higher than both Scappaticci et al.’s 13% and Kozloff et al.’s 4.4% rates, although these differences can be explained in part by both differences in WHC definition and tumor type (RCC vs. mCRC) and procedure (cytoreductive nephrectomy vs. hepatic metastectomy).

The results from the two “Poor” studies are highly uncertain and should be interpreted with utmost caution if used at all. Clark et al. observed an overall WHC incidence that was higher in the neoadjuvant setting (34.8%) than the adjuvant (5.6%), in agreement with Scappaticci et al. Golshan et al. reported a 43% WHC incidence after neoadjuvant bevacizumab that was not significantly different (p = 0.82) than the 39% rate after neoadjuvant cisplatin alone.
**Discussion**

VEGF-targeted therapies, including the anti-VEGF antibody bevacizumab, are increasingly being investigated and utilized in the treatment of various advanced-stage malignancies, reflecting the growing understanding of VEGF-mediated angiogenesis in tumor survival and growth. However, as VEGF also mediates many normal physiological processes, including the vasodilation, increased vascular permeability, and angiogenesis necessary for proper wound healing, such bevacizumab use can be expected to lead to impaired wound healing and other wound-healing complications. The WHC risk confers special clinical significance as bevacizumab is employed in both neoadjuvant and adjuvant settings before and/or after surgical resection, and its anti-VEGF activity may impair wound healing of both primary and surrounding surgical incisions. This delay in wound healing may impair patient quality of life and in turn lead to serious sequelae including infection, hemorrhage, fasciitis, osteomyelitis, gross necrosis, and flap and/or reconstruction loss. In addition, it necessarily delays clinical benefit from resumption of bevacizumab therapy. Therefore, this systematic review is an attempt to survey the current clinical evidence and assess the incidence, timing, and nature of bevacizumab-related wound-healing complications. Such considerations should guide clinical judgment of timing of bevacizumab therapy and management decisions for bevacizumab-related WHCs.

Of the eight articles included in final analysis, two were judged to be “Good” quality and another three to be “Fair”. The emerging consensus from the “Good” articles (Scappaticci *et al.*, Allegra *et al.*) stipulates that bevacizumab does appear to raise the WHC risk more than chemotherapy alone, and that neoadjuvant bevacizumab appears to raise the WHC risk more than adjuvant bevacizumab. However, two considerations should be taken into account about these conclusions.

First, the magnitude of these increases is less certain. Both the “Good” articles (Scappaticci *et al.*, Allegra *et al.*) reported similar WHC rates following adjuvant bevacizumab
use (1.3% vs. 1.7%), using the same WHC definition (CTCAEv3.0) in the same clinical setting (hepatic resection for metastatic colorectal cancer). Moreover, Allegra et al. observed a 1.7% WHC rate after adjuvant bevacizumab that was statistically-significantly different than the 0.3% rate after adjuvant chemotherapy alone; however, the absolute increase in risk here is small, such that the clinical significance of increased WHC risk may not be as prominent. In addition, Scappaticci et al. observed a significant increase in WHC risk from neoadjuvant over adjuvant bevacizumab use (13% vs. 1.3%). Clark et al. agreed with this conclusion, but with a far greater increase (35% vs. 6%).

Second, the applicability of these conclusions to other oncological indications with other WHC definitions is far less certain. Both “Good” articles employed the CTCAEv3.0 WHC criteria in patients with colorectal cancer. These conclusions cannot necessarily be generalized to breast cancer, renal cell carcinoma, glioblastoma multiforme, or non-small cell lung cancer. In fact, the other included studies performed in these indications sometimes found differing and opposing results. For example, both Golshan et al. (breast cancer) and Kesmodel et al. (stage IV colorectal cancer) did not find a significant difference in WHC incidence between bevacizumab versus chemotherapy alone, in disagreement with Allegra et al. (stage II and III colorectal cancer). Also, Jonasch et al. (cytoreductive nephrectomy for RCC) observed a higher WHC incidence after neoadjuvant bevacizumab than Scappaticci et al. (hepatic metastectomy for mCRC). While these studies were judged to be less quality and their results should consequently be interpreted with more uncertainty, it is important not to over-generalize results from the “Good” studies.

Some of the difference in observed WHC risk between studies is attributable to varying definitions of what constitutes a wound-healing complication. While the CTCAEv3.0 provides a systematic and consistent guideline that was independently derived and therefore reduces measurement bias, it is not necessarily the best applicable in all settings. WHC criteria should differ by indication according to clinical significance and potential sequelae. For example, since
the incision for hepatic resection occurs in the abdomen, it is justifiable to consider an incisional hernia as a WHC here, though certainly not for a craniotomy incision occurring in the scalp. Conversely, a poorly-healing craniotomy wound may produce osteomyelitis, CSF leakage, and meningoencephalitis, rendering it justifiable to include these as pertinent WHCs in this setting but not in others. Thus, the specific criteria for wound-healing complications cannot be standardized across oncological indications, as each indication results in a different procedure for surgical resection, with an incision that differs by location and size, and a different profile of potentially-harmful sequelae secondary to impaired wound-healing. As such, meta-analysis of WHC risk across indication remains not possible.

WHC criteria should be defined for future research purposes. Ideally, these criteria should be standardized within each oncological indication, independently-constructed by groups or committees other than the researching investigator, explicitly defined before initiation of the study, applied consistently to cases and controls, and as objective as possible, to minimize measurement bias. Furthermore, there should be some grading of WHCs to also report the severe complications, as is currently done in the CTCAEv3.0. Wound-healing complications can range from the somewhat mild (such as delayed wound-healing) to the very severe (such as skull flap necrosis producing meningoencephalitis), and it would be very helpful for providers to know both the rate of overall WHC and the rate of severe WHC when considering the toxicity profile of bevacizumab therapy.

Many variables can confound the relationship between treatment and wound-healing. This review tried to systematically organize them into three categories: patient variables, tumor variables, and procedural variables. Several of the included studies attempted to methodically report and control for these potential confounders, thus strengthening their final analysis, while other studies simply ignored them, making their reported WHC risk far less attributable to the presence of bevacizumab. Future research should consider these potential confounders when
trying to assess the bevacizumab-related WHC risk, especially in the setting of oncological patients, many of whom suffer from high and complex comorbidity.

General recommendations have already been provided regarding timing of bevacizumab therapy and onset of surgical intervention: bevacizumab therapy should occur at least 60 days before or 28 days after surgery[7, 33], should not be initiated until all surgical wounds are fully healed[7], and should be permanently discontinued if wound dehiscence occurs.[20] Bevacizumab treatment should also be withheld prior to elective surgery, though the interval here has not yet been optimized, with some recommending 4 weeks[7] and others 6-8 weeks.[38] These recommendations rely chiefly on preclinical pathophysiological evidence, as bevacizumab’s long circulating half-life of ~20 days[5] necessitates an appropriate interval between treatment cessation and surgery to adequately prevent toxicities resulting from inhibition of VEGF-mediated physiological processes, including wound-healing complications.

Thus, surgical oncologists apply conservative estimates of the bevacizumab-surgery interval, though these recommendations are not based on current clinical evidence. Importantly, it should be noted that any clinical benefit obtained by extending this interval and delaying bevacizumab therapy to minimize toxicity is necessarily offset by loss of bevacizumab’s therapeutic anti-tumor potential. Therefore, optimizing the duration of the bevacizumab-surgery interval remains an important goal for current and future research. None of the included studies specifically examined how the duration of this interval correlated with WHC risk.

The current clinical evidence is unfortunately not of high enough quality to change or refine these management guidelines. Future research is required to assess the WHC risk of neoadjuvant and adjuvant bevacizumab therapy and to compare these risks to that of chemotherapy alone within each oncological indication. Future research is also required to evaluate how the duration of the bevacizumab-surgery interval correlates with increased WHC risk, if at all. Ideally, such studies would consist of prospective and high-powered trials within each of bevacizumab’s five oncological indications that compares the WHC incidence between
cases (patients who received bevacizumab) and controls (patients who didn’t). Furthermore, such studies should control for confounding (Table 4), either by multivariate analysis or ideally through randomization. In addition, such studies should employ clearly-defined, independently-constructed WHC criteria that include some grading scheme to specify severe WHCs as well. Until then, the decision to proceed with surgical wound repair a certain time after bevacizumab cessation should depend on the clinical judgment and expertise of the managing multi-disciplinary team (including both plastic surgeons and oncologists) that weighs the potential costs of preventable bevacizumab-associated toxicities against the potential anti-tumor benefits of bevacizumab use, along with knowledge of the patient’s underlying characteristics and expressed wishes, and not on a prefixed length that does not consider contextual specifics.
Works Cited


