

Review

Hemorrhagic Complications in Gastric Cancer: Current Evidence and Multidisciplinary Management Strategies

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Simple Summary

Gastric cancer is one of the leading causes of cancer-related death worldwide, and tumor-associated bleeding represents one of its most immediately life-threatening complications. Critically, hemorrhage not only endangers life—it disrupts the entire oncologic treatment trajectory by delaying chemotherapy and diminishing performance status, trapping patients in a cycle where untreated disease fuels further bleeding. This review synthesizes two decades of evidence into a practical, multidisciplinary management framework. We describe a hemodynamic-guided stepwise algorithm: endoscopic hemostasis as the first-line approach, transcatheter arterial embolization for unstable patients or endoscopic failure, palliative radiotherapy as an effective non-invasive alternative, and surgery when all else fails. Crucially, we reframe the goal of hemorrhage control: stopping the bleeding is not the endpoint—it is the gateway to anticancer therapy, which is the true determinant of survival. We also identify key evidence gaps and propose priorities for future randomized trials.

Abstract

Hemorrhage is a clinically important emergency in gastric cancer, occurring in an estimated 3–36% of patients (with the incidence varying substantially by disease stage, tumor morphology, and the operational definition of hemorrhage applied), and potentially becoming life-threatening within 24 h. This review synthesizes evidence from the past two decades to propose a multidisciplinary, stepwise framework for managing gastric cancer-associated bleeding. Endoscopic hemostasis remains the first-line intervention and achieves initial bleeding control in 83–92.9% of cases, although 30-day rebleeding occurs in up to 28–41%. Transcatheter arterial embolization is an important option for persistent bleeding or hemodynamic instability, with a reported clinical success of approximately 72%. Palliative radiotherapy provides effective hemostasis in 68–88.5% of cases, and a biologically effective dose (BED10) exceeding 39 Gy may improve bleeding control. Surgery should be individualized according to disease stage, resectability, physiological reserve, and treatment intent, ranging from emergency vessel ligation to curative resection. Importantly, hemostasis should be regarded not as a final endpoint but as a therapeutic bridge enabling definitive anticancer therapy. Successful bleeding control followed by systemic chemotherapy is associated with improved overall survival. Management therefore requires coordinated decision-making among gastroenterology, interventional radiology, surgery, radiation oncology, and medical oncology teams.



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1. Introduction

Gastric cancer ranks fifth globally in cancer incidence and fifth in cancer-related mortality. According to GLOBOCAN 2022, an estimated 968,000 new cases and 660,000 deaths occurred worldwide in 2022, with age-standardized incidence and mortality rates of 9.2 and 6.1 per 100,000 persons, respectively [1]. The absolute burden is projected to rise by more than 50% by 2050, with East Asian countries—including the Republic of Korea, Japan, and China—bearing a disproportionate share of this burden [1].

Clinically significant hemorrhage occurs as a complication in an estimated 3–36% of gastric cancer patients—with the reported incidence varying substantially depending on disease stage, tumor morphology, treatment setting, and the operational definition of hemorrhage applied [2–6]. In a large-scale retrospective analysis of the United States National Inpatient Sample database (2016–2018), Minhem et al. reported a gastrointestinal hemorrhage prevalence of 15.7% among hospitalized patients with gastric cancer [5]. A tertiary-center retrospective cohort study from Thailand identified upper gastrointestinal bleeding in 36.1% of gastric cancer patients, the majority of whom presented at an advanced stage [6]. Regardless of the precise figure, hemorrhagic complications represent one of the most immediately life-threatening oncologic emergencies encountered in the management of gastric cancer.

The consequences of tumor hemorrhage extend well beyond the acute hemodynamic insult. Active bleeding delays the initiation of systemic anticancer therapy, diminishes performance status, and predisposes patients to transfusion-related morbidity, effectively severing access to potentially life-prolonging treatment. Among patients who experience rebleeding, median overall survival is significantly shorter than in those without recurrence (2.7 vs. 3.9 months; $p = 0.02$) [2]. Early rebleeding, defined as recurrence within 72 h of initial hemostasis, is associated with the most dismal prognosis, with a median survival of only 1.0 month—compared with 3.1 months for late rebleeding and 4.3 months for patients who remain bleed-free [2].

The stepwise management of gastric cancer-associated bleeding follows a structured, multidisciplinary algorithm: endoscopic hemostasis serves as the first-line intervention; transcatheter arterial embolization (TAE) or palliative radiotherapy is considered upon failure; and surgical intervention is pursued when patient status permits. This review synthesizes the evidence published over the past two decades to provide a clinically actionable framework for managing hemorrhagic complications across disease stages and patient subgroups.

2. Epidemiology and Pathophysiology of Tumor Bleeding in Gastric Cancer

2.1. Incidence and Clinical Spectrum

Hemorrhagic complications in gastric cancer span a wide clinical spectrum, from insidious chronic blood loss presenting as iron-deficiency anemia to acute, life-threatening upper gastrointestinal hemorrhage. Notably, approximately 77% of patients with gastrointestinal malignancies first present with bleeding as their index symptom, underscoring the diagnostic centrality of early endoscopic evaluation [4]. Acute hemorrhage typically manifests as melena (approximately 75% of cases) or hematemesis (approximately 50%); these presentations are not mutually exclusive, as both may occur concurrently within a single

hemorrhagic episode. Whereas chronic bleeding follows an indolent course characterized by progressive fatigue, anorexia, and iron-deficiency anemia—a pattern particularly common in antral and lesser-curvature lesions. On endoscopy, oozing hemorrhage represents the most frequently observed hemorrhagic phenotype.

2.2. Pathophysiology of Tumor-Associated Hemorrhage

The biology of gastric cancer bleeding is fundamentally distinct from that of benign peptic ulcer hemorrhage. As the neoplasm expands, progressive microenvironmental changes—hypoxia, acidosis, elevated interstitial fluid pressure, and nutrient deprivation—drive pathological angiogenesis. A particularly sinister mechanism is vasculogenic mimicry, whereby highly aggressive cancer cells independently generate vascular-like channels lacking both pericyte investment and basement membrane integrity [3]. These structurally deficient vessels are prone to spontaneous rupture, and tumor necrosis further exposes submucosal vessels directly to the gastric lumen, creating additional bleeding foci that resist conventional hemostatic mechanisms.

Systemic coagulopathy amplifies the hemorrhagic diathesis. Advanced gastric cancer is frequently associated with chronic, low-grade disseminated intravascular coagulation (DIC), progressive thrombocytopenia, and impaired platelet function. Patient-level risk factors include advanced age, hypertension, chronic renal failure, active *H. pylori* infection, and concurrent use of antithrombotic or anticoagulant agents—a particularly relevant consideration in the aging oncologic population.

2.3. Predictors of Rebleeding and Prognostic Impact

Massive transfusion—defined as the administration of five or more units of packed red blood cells—is the sole independent predictor of early rebleeding (OR 4.75; 95% CI, 1.45–15.57) [2,7]. This relationship is clinically paradoxical: the patients with the most catastrophic bleeding are precisely those at highest risk for hemostatic failure after initial treatment. Early rebleeding (within 72 h) portends a median survival of only 1.0 month, starkly inferior to late rebleeding (3.1 months) and no rebleeding (4.3 months) [2]. Because rebleeding forecloses access to subsequent chemotherapy and accelerates disease progression, aggressive, anticipatory management of high-risk patients is essential. These prognostic data collectively underpin the rationale for the stepwise treatment algorithm presented in Section 4: every management decision must be oriented not merely toward achieving hemostasis but toward preserving the opportunity for subsequent systemic anticancer therapy.

3. Clinical Presentation and Initial Assessment

3.1. Initial Resuscitation and Transfusion Strategy

Initial management of hemorrhagic gastric cancer follows standard upper gastrointestinal bleeding protocols, with important modifications for the oncologic context. Hemodynamic assessment, large-bore intravenous access, complete blood count (including hemoglobin), and coagulation studies should be obtained immediately. Platelet correction to $\geq 40,000/\text{mm}^3$ is recommended prior to endoscopy. In patients with persistent hematemesis, hypoxia, or altered consciousness, urgent airway management—including endotracheal intubation—must precede endoscopic intervention.

The landmark randomized controlled trial by Villanueva et al. established the decisive evidence base for transfusion thresholds in acute upper gastrointestinal bleeding [8]. A restrictive transfusion strategy—withholding red cell transfusion until hemoglobin falls below 7 g/dL—reduced mortality and rebleeding rates by 35% and 42%, respectively, compared with a liberal strategy (threshold 9 g/dL) [8]. The ACG Clinical Guideline on Upper

Gastrointestinal and Ulcer Bleeding issues a conditional recommendation for a restrictive transfusion threshold of Hb 7 g/dL in hospitalized patients with upper gastrointestinal bleeding [9]. The ESGE Guideline Update 2021 issues a strong recommendation for the same threshold in hemodynamically stable patients without cardiovascular disease (moderate quality evidence) [10]. Both guidelines note that a higher threshold (Hb 8–9 g/dL) should be considered in hemodynamically unstable patients or those with significant cardiovascular comorbidity.

3.2. Management of Anticoagulant and Antiplatelet Agents

A clinically significant proportion of gastric cancer patients receive concurrent antithrombotic or anticoagulant therapy for cardiovascular indications, and their management during acute tumor-related hemorrhage requires individualized assessment balancing bleeding risk against thrombotic risk, in accordance with the ACG–CAG Clinical Practice Guideline [11]. For patients on vitamin K antagonists (e.g., warfarin), urgent reversal with intravenous vitamin K combined with four-factor prothrombin complex concentrate (4F-PCC) is recommended when the INR is supratherapeutic in the setting of active hemorrhage; 4F-PCC is preferred over fresh frozen plasma (FFP) due to more rapid reversal kinetics. For patients receiving direct oral anticoagulants (DOACs), specific reversal agents should be considered in life-threatening hemorrhage: idarucizumab for dabigatran, and andexanet alfa for factor Xa inhibitors (apixaban, rivaroxaban, edoxaban), in accordance with the most recent ISTH guidance [12]. In settings where specific reversal agents are unavailable, 4F-PCC may be considered as a non-specific alternative. Antiplatelet agents should generally be withheld during active bleeding; however, in patients with recent coronary artery stent placement, urgent cardiology consultation is essential before discontinuation. Once active hemorrhage has been controlled, VTE prophylaxis should be resumed promptly, as hospitalized cancer patients carry an inherently elevated thrombotic risk. The 2023 ASCO Clinical Practice Guideline recommends pharmacologic thromboprophylaxis with LMWH for most hospitalized cancer patients with acute medical illness [13]. The optimal timing of anticoagulation resumption following hemostasis should be determined collaboratively within the multidisciplinary team.

3.3. Risk Stratification

Conventional risk stratification tools—the Glasgow-Blatchford Score (GBS), Rockall Score, and AIMS65—demonstrate limited discriminatory power in the pre-endoscopic setting for tumor-related bleeding. In a landmark study of 357 patients with inoperable gastric cancer from the National Cancer Center, Republic of Korea, the complete Rockall Score (incorporating endoscopic findings) outperformed the GBS in predicting the need for urgent intervention (AUC 0.78 vs. 0.56), with Forrest class Ia–IIb stigmata of recent hemorrhage identified as significant independent predictors of urgent intervention [14]. These findings underscore that risk stratification in tumor bleeding must integrate clinical parameters with endoscopic findings—reinforcing the imperative for early endoscopy. Beyond validated hemorrhage risk scoring systems, a comprehensive set of cancer-specific patient factors must be systematically assessed to guide individualized treatment decisions. Performance status (ECOG PS), disease stage, tumor burden, serum albumin (hypoalbuminemia < 3.0 g/dL), nutritional status, sarcopenia (assessed by L3 skeletal muscle index on CT), frailty (Clinical Frailty Scale or Fried phenotype), ASA physical status, and the Charlson Comorbidity Index (CCI) should be evaluated in parallel with hemorrhage-specific risk scores as part of the multidisciplinary assessment. Sarcopenia, in particular, has been identified as an independent predictor of postoperative surgical morbidity and

inferior survival in gastric cancer patients [15,16], and should be specifically evaluated when surgical intervention is contemplated.

3.4. Role of Proton Pump Inhibitors

Despite their well-established role in benign peptic ulcer bleeding, proton pump inhibitors (PPIs) have not demonstrated independent hemostatic efficacy in gastric cancer-related tumor bleeding. The only randomized controlled trial directly evaluating this question compared oral lansoprazole with placebo in patients with inoperable gastric cancer, finding no significant difference in tumor bleeding incidence (7.8% vs. 9.5%) [14]. It should be noted that intravenous PPI has not been formally evaluated in this tumor-specific bleeding context. Its inclusion in the initial resuscitation algorithm (Figure 1) reflects standard empirical practice in the acute emergency setting, where general upper gastrointestinal bleeding guidelines are followed prior to endoscopic confirmation of the bleeding source. Once tumor-related bleeding is confirmed endoscopically, PPI therapy does not provide meaningful independent hemostatic benefit and should not be regarded as a substitute for tumor-directed intervention. This reflects the fundamentally distinct pathophysiology of tumor hemorrhage, in which acid-independent mechanisms—vascular fragility, tumor necrosis, and coagulopathy—predominate.

4. Treatment Algorithm

The management of gastric cancer-associated bleeding is stratified according to the initial hemodynamic status of the patient. Figure 1 presents a proposed expert-opinion-based stepwise framework synthesized from the body of evidence reviewed in this article. As no universally validated or guideline-endorsed algorithm currently exists for this clinical scenario, Figure 1 should be interpreted as a practical clinical reference rather than a formally established recommendation; its application must be individualized according to institutional resources, tumor characteristics, bleeding morphology, and patient performance status. The fundamental concept underlying this framework is that hemostatic control is not a therapeutic endpoint, but rather a gateway to subsequent anticancer therapy—enabling chemotherapy or curative resection and thereby translating hemostatic success into meaningful survival benefit.

Pathway 1—Hemodynamically Unstable Patients

Following immediate resuscitation (transfusion, intravenous fluid replacement, and intravenous PPI), emergency TAE is generally favored as the first-line hemostatic intervention based on available retrospective evidence. If TAE achieves initial hemostasis but rebleeding recurs, emergency surgery (vessel ligation or palliative gastrectomy) is indicated. In patients with refractory rebleeding after multiple interventions, palliative radiotherapy serves as an additional hemostatic option.

Pathway 2—Hemodynamically Stable Patients

In hemodynamically stable patients, the choice of initial hemostatic modality depends on tumor characteristics assessed at the time of endoscopy—morphology, bleeding source accessibility, and likelihood of durable hemostasis—rather than following a rigid linear sequence. Following tumor evaluation, the algorithm branches into two routes based on lesion morphology:

- **Focal lesion:** When the bleeding source is focal and endoscopically accessible, endoscopic hemostasis (APC, clipping, epinephrine injection, or hemostatic powder [TC-325]) is the recommended first-line approach. If rebleeding occurs after endoscopic hemostasis, TAE should be considered as the next step before surgical escalation (red arrow)—emergency surgery is not the immediate default.

- Diffuse lesion: For diffuse oozing from extensive or circumferential tumor surfaces, lesions in anatomically difficult locations, or when durable endoscopic hemostasis is judged unlikely, palliative radiotherapy (PR) may be selected as a primary modality without prior endoscopic attempt (orange solid arrow).

Combined sequential strategies—endoscopy → TAE → palliative radiotherapy—are applicable in refractory hemorrhage [17].

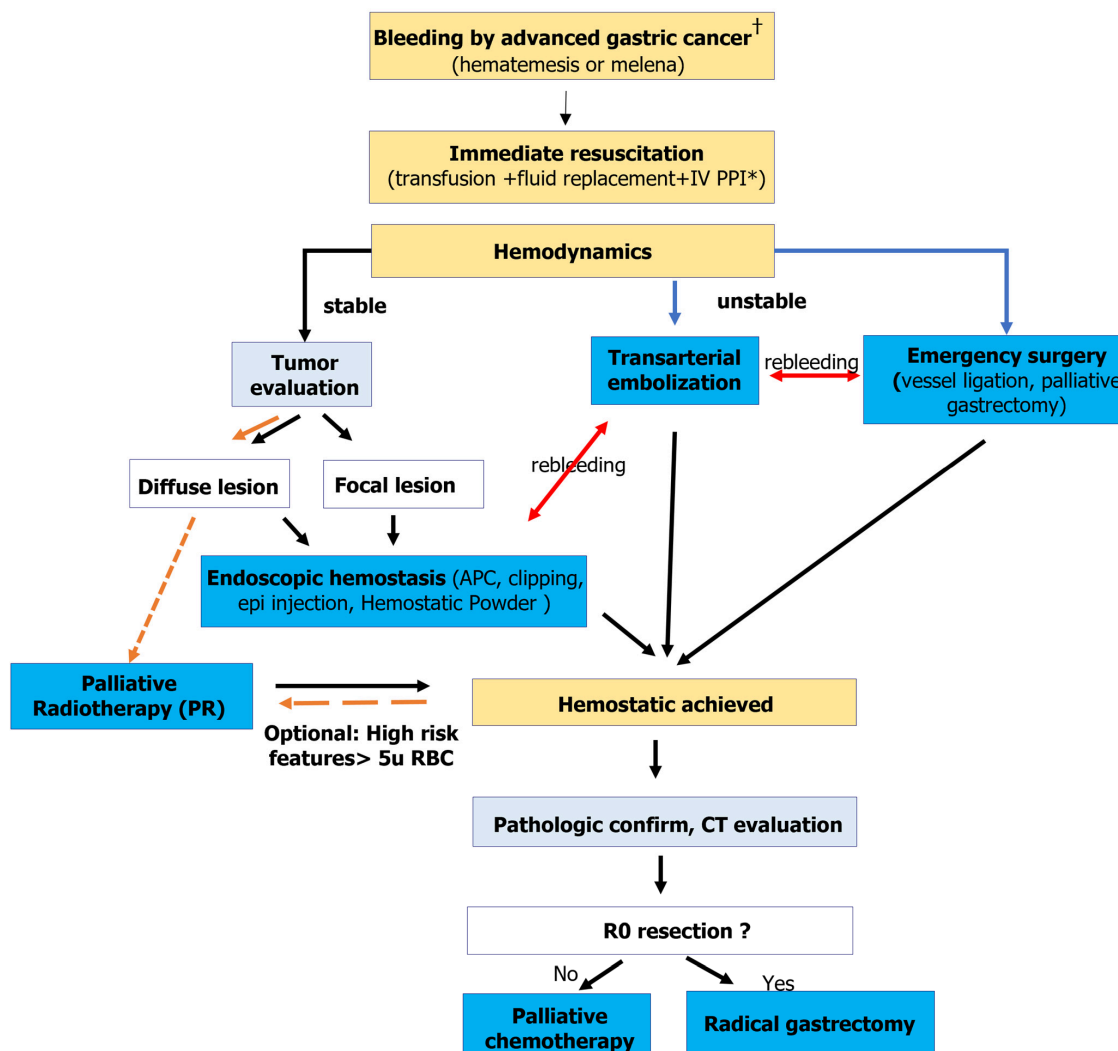


Figure 1. Proposed expert-opinion-based stepwise management algorithm for hemorrhagic complications in advanced gastric cancer. Arrow key: Black arrows, hemodynamically stable pathway; Blue arrows, hemodynamically unstable pathway; Red arrows, applicable upon rebleeding; Orange solid arrow, optional pathway based on tumor morphology assessment; Orange dashed arrows, optional intervention—recommended for diffuse lesions or high-risk features (transfusion ≥ 5 units pRBC). Abbreviations: TAE, transarterial embolization; APC, argon plasma coagulation; PR, palliative radiotherapy; RBC, red blood cells; CT, computed tomography. * IV PPI is administered empirically as part of initial resuscitation per standard upper gastrointestinal bleeding guidelines, pending endoscopic confirmation of the bleeding source. Once a tumor origin is confirmed, PPI does not provide independent hemostatic benefit and should not substitute for tumor-directed therapy. [†] This algorithm represents a proposed expert-opinion-based clinical framework and does not constitute a formally validated or guideline-endorsed management protocol. Clinical application should be individualized based on institutional resources, tumor characteristics, bleeding morphology, and patient performance status.

Pre-Emptive Management of High-Risk Patients

In patients with identified high-risk features for rebleeding—transfusion requirement ≥ 5 units, Forrest class Ia/IIa lesions, lesion diameter > 2 cm, or active bleeding on angiography—early adjunctive palliative radiotherapy (BED10 ≥ 39 Gy) should be considered even after successful initial hemostasis, to reduce the probability of rebleeding and preserve the opportunity for systemic therapy.

Key Point: Every step in this algorithm must serve a single purpose—restoring the patient’s eligibility for anticancer therapy. Hemorrhage control is the prerequisite, not the objective; the therapeutic window it creates must be immediately leveraged to initiate systemic treatment.

5. Endoscopic Hemostasis

Endoscopic hemostasis is the cornerstone of first-line management in hemodynamically stable patients with gastric cancer-related bleeding, offering the unique advantage of simultaneous diagnostic evaluation and therapeutic intervention. The Forrest classification of recent hemorrhage stigmata retains utility for procedural decision-making and rebleeding risk stratification in the tumor-bleeding context. However, unlike benign peptic ulcer bleeding, the 30-day rebleeding rate following initial endoscopic hemostasis in gastric cancer ranges from 28% to 41%—dramatically higher than that observed after ulcer hemostasis—reflecting the structural vulnerability of tumor vasculature [2,7].

In a retrospective cohort of 113 patients with inoperable advanced gastric cancer, initial hemostasis was achieved in 92.9% of cases, yet the 3-day early rebleeding rate was 18.1% and the 30-day rebleeding rate was 29.5% [7]. Electrocoagulation was the predominant modality (92.0% of procedures), with combination therapy required in 30.1%. A separate cohort reported an initial hemostasis rate of 83% with a 30-day rebleeding rate of 28.3% [2]. Across both studies, transfusion of five or more packed RBC units emerged as the sole independent predictor of early rebleeding, establishing a clinically actionable threshold for escalating to more definitive hemostatic strategies.

5.1. Hemostatic Modalities

- **Injection therapy:** Diluted epinephrine (1:10,000 in normal saline) is widely used for its vasoconstrictive and tamponade effects, and has been employed in approximately 37.7% of endoscopic sessions for gastric cancer-related bleeding in published cohorts [18]. However, epinephrine monotherapy is associated with substantially higher rebleeding rates compared with combination therapy, and current guidelines caution against its use as monotherapy [18,19]. Epinephrine injection should be combined with thermal or mechanical modalities as standard practice.
- **Thermal therapy:** Electrocoagulation, APC, Coagrasper hemostatic forceps, and hot biopsy forceps are the principal thermal modalities. APC was used in approximately 77.4% of endoscopic sessions for gastric cancer-related bleeding in one large cohort [18], and is particularly well-suited to tumor bleeding because its non-contact delivery mode enables uniform coagulation across irregular, friable tumor surfaces (Figure 2). Martins BC et al. reported 100% initial hemostasis with APC in bleeding gastrointestinal malignancies, with significant reduction in transfusion requirements [20]. Evidence specific to gastric cancer in the advanced/unresectable setting is predominantly derived from the cohort studies described above [2,7,18].
- **Mechanical therapy:** Hemoclips and endoscopic loops are effective for focal vessel ligation. Hemoclippping was employed in approximately 25.5% of endoscopic sessions for gastric cancer bleeding in published cohorts [18]. However, their applicability is limited in gastric cancer by tumor tissue fragility and irregular surface morphology.

Lesion size > 2 cm has been identified as a significant independent predictor of endoscopic hemostatic failure (aOR 8.056; 95% CI, 1.329–48.846) [21], limiting clip-based approaches for large advanced gastric cancer lesions. The over-the-scope clip (OTSC) has been reported in isolated case reports as a rescue option for bleeding malignant gastric ulcers with large exposed vessels [22,23]; however, systematic evidence specific to gastric cancer is absent and OTSC should currently be considered investigational in this setting, given that many advanced gastric cancers present with diffuse, friable surfaces rather than a focal vessel amenable to clip-based occlusion.

- Combination therapy: Multimodal endoscopic approaches combining two or more of the above techniques are recommended for high-risk lesions and are increasingly recognized as the standard of care in tumor-related bleeding.

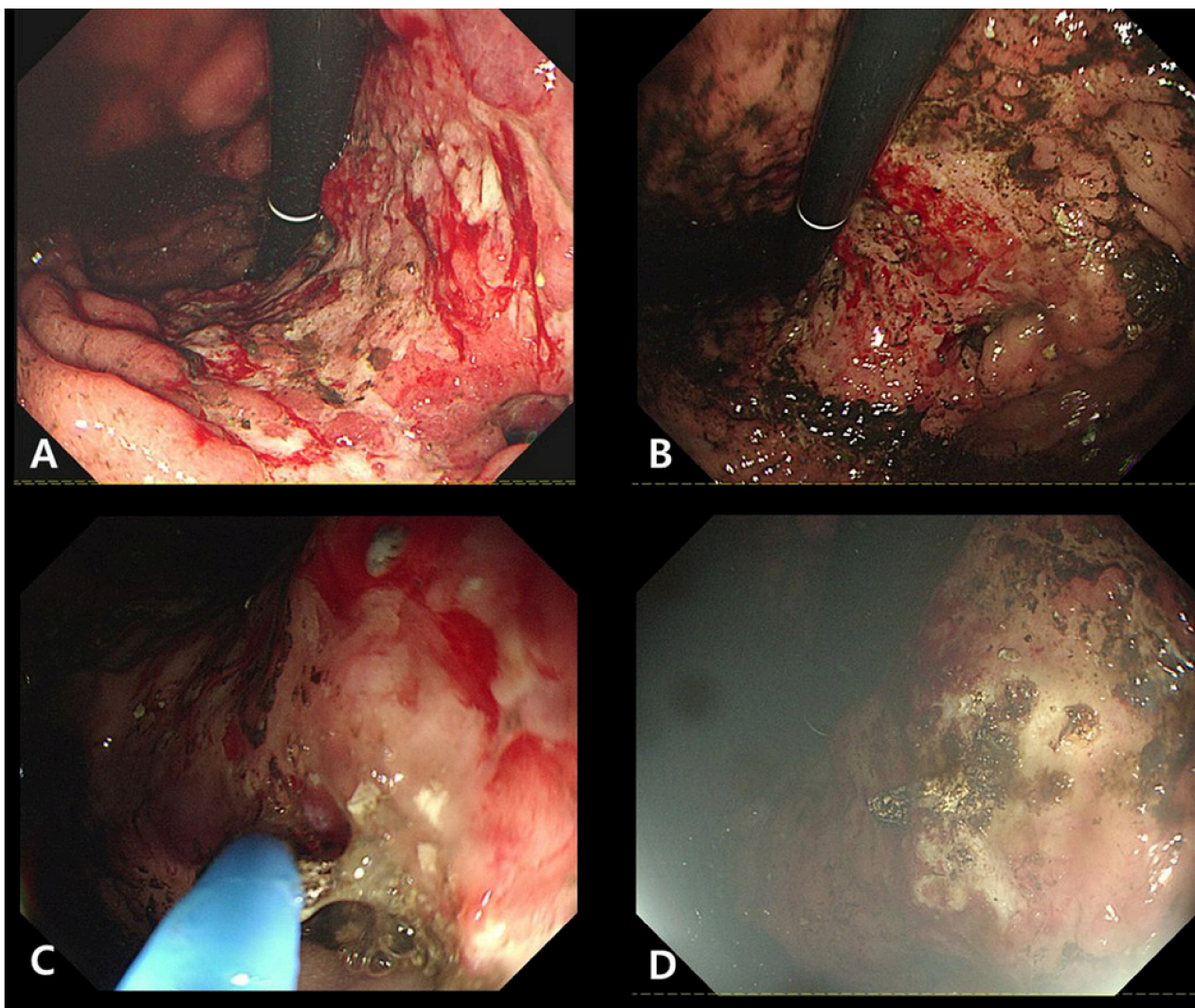


Figure 2. Endoscopic findings and hemostatic procedure in a patient with gastric cancer-related bleeding. (A) Active hemorrhage arising from a diffuse gastric carcinoma involving the lesser curvature. (B) Recurrent tumor bleeding on repeat endoscopy. (C) Endoscopic hemostasis using argon plasma coagulation (APC). (D) Successful hemostasis following APC treatment.

5.2. Hemostatic Powder

TC-325 (Hemospray; Cook Medical, Winston-Salem, NC, USA) represents a paradigm shift in the endoscopic management of tumor bleeding. Upon contact with blood, this mineral compound transforms into a cohesive, adhesive plug that mechanically occludes the bleeding surface and activates the coagulation cascade—a mechanism particularly

suited to the diffuse, surface-bleeding pattern characteristic of gastric tumors. Its non-contact spray delivery obviates the need for precise instrument positioning on friable tissue.

The pivotal evidence for TC-325 derives from a multicenter randomized controlled trial by Pittayanon et al., enrolling 106 patients with malignant gastrointestinal bleeding. TC-325 achieved a 30-day rebleeding rate of only 2.1%, compared with 21.3% in the standard endoscopic treatment (SET) group (OR 0.09; 95% CI, 0.01–0.80; $p = 0.003$), and immediate hemostasis was achieved in 100% versus 68.6%, respectively [24]. A meta-analysis of four randomized controlled trials ($N = 227$) corroborated these findings, demonstrating a significantly higher immediate hemostasis rate with TC-325 (RR 1.48; 95% CI, 1.26–1.74) [25]. Given its transient hemostatic action, TC-325 is best conceptualized as a bridging therapy—establishing hemodynamic stability prior to more definitive interventions such as TAE, radiotherapy, or surgery.

6. Transcatheter Arterial Embolization (TAE)

Based on predominantly retrospective evidence, TAE has been most commonly employed as a first-line hemostatic intervention for hemodynamically unstable patients and as a rescue option following endoscopic failure in stable patients (Level of Evidence: 4, OCEBM). Technical success is defined as angiographic achievement of vascular occlusion at the target vessel, confirmed by cessation of contrast extravasation. Clinical success is defined as sustained hemorrhage control without emergency surgery or repeat embolization within 30 days. The distinction between these two endpoints is clinically significant: a technically successful embolization may fail to achieve clinical success if collateral circulation reconstitutes bleeding from adjacent vessels—a scenario particularly prevalent in gastric cancer given the dual arterial supply of the stomach. As the supporting data are derived largely from single-institution retrospective series, these observations should be applied with clinical judgment rather than as formal guideline recommendations.

6.1. Clinical Outcomes

The most comprehensive synthesis of TAE outcomes in gastric cancer-associated bleeding is a 2024 systematic review and meta-analysis by Hall et al., incorporating seven retrospective studies [26]. Technical success was achieved in 94.9% of cases; clinical success—defined as sustained hemostasis without the need for emergency surgery—was 72% (95% CI, 66–79%); the rebleeding rate was 11%; major complication rate was 2.4%; and 30-day mortality was 26.4%, the large majority of which was attributable to underlying disease progression rather than procedural morbidity.

6.2. Predictors of TAE Failure and Embolic Agent Selection

Active bleeding on angiography ($p = 0.044$) and the need for massive transfusion ($p = 0.039$) are independent predictors of TAE failure; conversely, TAE success is itself a significant independent predictor of 30-day survival (multivariate OR 0.132; $p = 0.022$) [3]. This paradox—that the patients with the most severe hemorrhage are least likely to benefit from TAE—necessitates early contingency planning for surgical or radiotherapeutic rescue in these individuals.

Regarding embolic agent selection, gelatin sponge (Gelfoam) provides temporary vascular occlusion and carries a risk of recanalization with subsequent rebleeding, whereas *n*-butyl cyanoacrylate (NBCA) induces immediate, permanent occlusion but risks non-target embolization. Angiographic images during TAE for recurrent tumor bleeding in advanced gastric cancer are presented in Figure 3. A meta-analysis comparing coils with NBCA found no significant differences in clinical success, 30-day rebleeding, major complications, or

30-day mortality [26]. Advances in superselective microcatheter techniques enable increasingly precise vascular targeting, minimizing ischemic complications to non-target tissues.

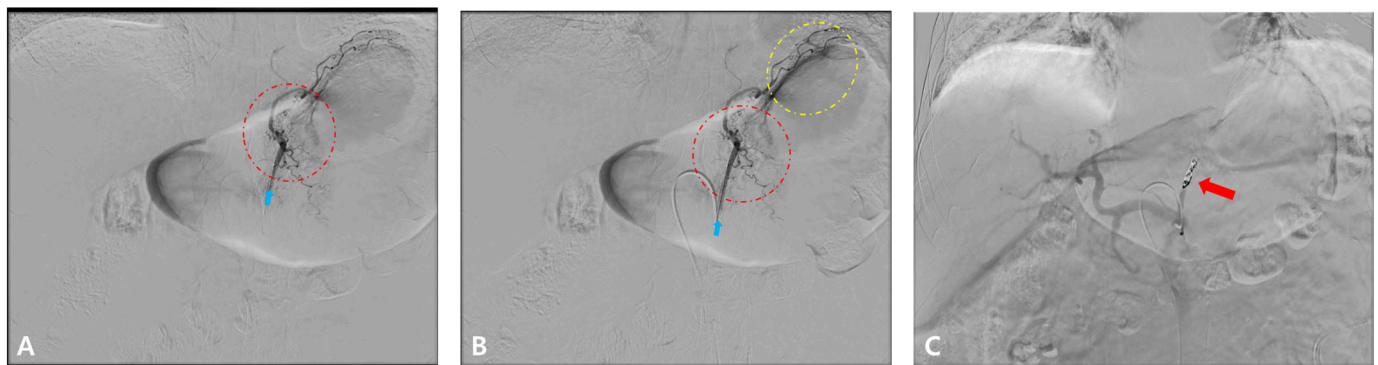


Figure 3. Angiographic images during transcatheter arterial embolization (TAE) for recurrent tumor bleeding in advanced gastric cancer. (A) Selective catheterization of the left gastric artery (blue arrow), with the red dashed circle delineating the arterial network supplying the tumor. (B) Active extravasation of contrast medium into the gastric lumen (yellow dashed circle), confirming the bleeding source. (C) Completion angiogram after deployment of coils (red arrow) and gelatin sponge for vascular occlusion.

7. Surgical Treatment

Surgical intervention occupies two distinct positions in the hemorrhagic gastric cancer algorithm. In the emergency setting, it is the definitive rescue maneuver for refractory hemorrhage following failed endoscopy and TAE. In the elective setting, following successful hemostasis and CT restaging, radical gastrectomy represents the optimal oncologic intervention for patients with resectable disease. These two contexts carry profoundly different risk profiles and expected outcomes.

7.1. Emergency Surgery—Indications and Risk Factors

In hemodynamically unstable patients in whom TAE is unavailable or has failed, emergency surgery becomes necessary. A two-step surgical strategy—initial hemorrhage control via suture ligation or vessel ligation, followed by staged definitive gastrectomy once the patient's condition has stabilized—is strongly preferred over immediate radical resection in the acute setting [27]. Emergency gastrectomy for gastric cancer is associated with substantially higher perioperative morbidity and mortality than elective resection: a nationwide Japanese database study (2012–2017) demonstrated that emergency colorectal and gastric cancer resection carried significantly higher 30-day mortality (OR 4.86–6.98) and overall complication rates (OR 1.68–2.18) compared with elective procedures (all $p < 0.001$).

Established risk factors for postoperative complications and mortality in this setting include age ≥ 65 years, hemoglobin < 10 g/dL, hypotension at admission, and cardiopulmonary complications during the postoperative period [27,28]. Emergency surgery should be reserved as a last resort when all endoscopic and interventional radiology options have been exhausted. It is important to recognize that emergency surgery for gastric cancer-related bleeding may need to simultaneously address concurrent complications. Gastric outlet obstruction (GOO) may coexist with bleeding, particularly in antral tumors; in such cases, surgical options include suture ligation combined with gastrojejunostomy bypass or palliative gastrectomy [29,30]. Palliative gastrectomy provides superior hemostatic outcomes compared to bypass in the tumor-bleeding group, while offering comparable outcomes in GOO [29]. For frank gastric perforation accompanying hemorrhage, a stomach-preserving strategy (peritoneal lavage and suture repair) has been reported as a feasible approach in patients with distant metastasis, permitting resumption of chemotherapy in

78% of cases [31]. All operative strategies must be determined intraoperatively and should ideally be planned within an MDT framework prior to surgery.

7.2. Curative vs. Palliative Resection—Tailoring the Indication

For stabilized patients with confirmed R0-resectable disease on CT restaging, radical gastrectomy is the ideal intervention, simultaneously achieving definitive hemostasis and oncologic cure. A systematic review and meta-analysis incorporating 128 studies and 58,675 patients demonstrated that palliative gastrectomy for advanced gastric cancer was associated with significantly improved one-year survival compared with non-resectional procedures and best supportive care, though at the cost of significantly higher overall complication rates (OR 2.14; 95% CI, 1.34–3.46) [32].

Survival benefit from palliative resection appears largely restricted to select patients: multivariate analyses identify ASA score ≤ 1 and receipt of postoperative chemotherapy as independent determinants of survival advantage, with positive lymph node count < 15 as an additional favorable predictor [32]. The landmark REGATTA trial provided an important counterpoint, demonstrating that gastrectomy plus chemotherapy offered no survival benefit over chemotherapy alone in patients with a single non-curable factor—a finding that tempers enthusiasm for non-curative resection [33].

Surgical candidacy must be evaluated through a multidimensional lens extending beyond hemodynamic stability alone. Favorable surgical indicators: ECOG PS 0–1; potentially R0-resectable disease on CT restaging; positive lymph node count < 15 ; serum albumin ≥ 3.0 g/dL; absence of significant sarcopenia (assessed by L3 skeletal muscle index on CT [15,16]); CCI ≤ 2 ; ASA class ≤ 2 ; anticipated eligibility for postoperative systemic chemotherapy. High-risk surgical indicators: Age ≥ 65 years; Hb < 10 g/dL; preoperative hypotension; cardiopulmonary comorbidities; serum albumin < 3.0 g/dL; significant sarcopenia; clinical frailty (CFS ≥ 5); CCI ≥ 3 ; ASA class ≥ 3 ; multiple distant metastases; peritoneal dissemination; ECOG PS ≥ 3 . When multiple high-risk indicators co-exist, the two-step surgical strategy—initial hemorrhage control via TAE or endoscopy, followed by staged elective resection after nutritional optimization—is strongly preferred over emergency gastrectomy [15,16].

8. Palliative Radiotherapy

Palliative radiotherapy has emerged as a legitimate and effective hemostatic intervention for patients with surgically unresectable advanced gastric cancer complicated by severe hemorrhage. It is applicable when endoscopic therapy or TAE fails or is contraindicated, and when the patient's performance status precludes repetitive invasive procedures. In addition, for patients with diffuse or anatomically inaccessible lesions in whom durable endoscopic hemostasis is judged unlikely, palliative radiotherapy may be considered as a primary hemostatic modality without prior endoscopic attempt, as delineated in the treatment algorithm (Figure 1). Radiotherapy achieves hemostasis through radiation-induced endothelial damage to tumor-feeding vessels, promoting thrombosis and fibrous obliteration of the bleeding source. A further advantage over endoscopic and interventional approaches is the feasibility of re-irradiation in the setting of rebleeding.

8.1. Hemostatic Efficacy

The Asan Medical Center cohort (2002–2018; $n = 61$), treated with a median dose of 30 Gy using 3D-CRT technique, achieved a hemostatic success rate of 88.5%, with significant hemoglobin elevation and reduction in transfusion requirements [34]. Kondoh et al. reported that 11 of 15 patients (73%) achieved hemostasis at a median of 2 days after treatment initiation [35]. Lee et al., in a retrospective study conducted at Daejeon St. Mary's

Hospital, Republic of Korea (n = 42), reported hemostatic efficacy in 69.0% of patients, with a BED₁₀ of 36 Gy identified as the optimal discriminating threshold between responders and non-responders [36]. A multi-institutional retrospective study by Takeda et al., incorporating data from multiple Japanese institutions (n = 117; 120 treatment courses), reported an overall hemostatic success rate of 59.6%, with BED₁₀ identified as the sole independent predictor of hemostatic response on multivariate analysis [37]. Across published retrospective series, overall hemostatic efficacy is estimated at 68–88.5%, with a median post-treatment survival of approximately 3 months. As all available data derive from retrospective studies—predominantly from East Asian centers—these estimates should be interpreted in light of the limitations outlined in Section 10.

8.2. Dose Fractionation and BED Thresholds

While an optimal dose fractionation regimen has not been formally standardized, BED₁₀ has emerged as the principal dosimetric determinant of hemostatic response. A BED₁₀ of 36 Gy has been identified as the optimal discriminating threshold between responders and non-responders [36]. A study employing blood transfusion-free survival (BTFS) as the primary endpoint found that the 30 Gy/10-fraction regimen (BED₁₀ 39 Gy) achieved a one-year BTFS of 78%, significantly superior to the 40 Gy/20-fraction regimen (25%; *p* = 0.03) [37]. Short-course low-dose regimens (6 Gy in 3 fractions—LSP-RT) remain a pragmatic option for patients with poor performance status, offering the additional advantages of abbreviated hospitalization and preserved feasibility of re-irradiation upon rebleeding [38].

8.3. Hemostasis as a Bridge to Systemic Therapy

Perhaps the most clinically compelling rationale for pursuing radiotherapeutic hemostasis is its capacity to unlock access to systemic anticancer treatment. In a cohort analysis by Yagi et al., patients who received post-hemostasis chemotherapy achieved a median overall survival of 6.5 months, compared with only 1.6 months in those who did not (*p* = 0.001) [39]. Hemostatic success itself was an independent survival predictor: patients with successful radiotherapeutic hemostasis demonstrated significantly longer overall survival than non-responders (*p* = 0.0026) [34]. Acute radiotherapy-related toxicity is predominantly Grade 1–2 (nausea, fatigue, anorexia); Grade ≥ 3 toxicity occurs in fewer than 10% of patients, though isolated cases of gastric perforation have been reported with 3D-CRT, warranting caution in patients with deeply infiltrating tumors [40] (Table 1).

Table 1. Summary of treatment modalities for gastric cancer-associated bleeding: key outcomes and level of evidence.

Treatment Modality	Study Type	Key Studies (n)	Initial Hemostasis Rate	30-Day Rebleeding Rate	Median Overall Survival	Major Complications	Level of Evidence (OCEBM)
Endoscopic hemostasis	Retrospective cohort	Kim YI 2013 (n = 113) [2]; Song JJ 2017 (n = 106) [7]	83–92.9%	28–41%	2.7–4.3 months (varies by rebleeding status)	<5%	4
TC-325 (Hemospray)	RCT; meta-analysis of RCTs	Pittayanon 2018 (n = 106) [24]; Saeed 2024 (n = 227) [25]	97.7–100%	2.1–17%	Not reported	Rare (perforation reported)	1b
Transcatheter arterial embolization (TAE)	Systematic review/meta-analysis (retrospective studies)	Hall 2024 [26]	94.9% (technical); 72% (clinical)	11%	~38 days	2.4% (major)	3a

Table 1. Cont.

Treatment Modality	Study Type	Key Studies (n)	Initial Hemostasis Rate	30-Day Rebleeding Rate	Median Overall Survival	Major Complications	Level of Evidence (OCEBM)
Palliative radiotherapy	Retrospective cohort; multi-institutional study	Yu 2021 (n = 61) [34]; Takeda 2022 [37]	68–88.5%	Not reported	~3 months	<10% Grade $\geq$ 3	4
Emergency surgery	Retrospective; nationwide database	Kasakura 2002 [27]; Lee 2006 [28]	~75–85% (hemorrhage control)	Not reported	Variable	Significantly higher than elective surgery (OR 4.86–6.98)	4
Radical gastrectomy (elective)	Systematic review/meta-analysis	Cowling 2021 (n = 58,675) [32]	—	—	12.8 months (palliative resection)	OR 2.14 vs. non-resection	3a

RCT, randomized controlled trial; OCEBM, Oxford Centre for Evidence-Based Medicine; OR, odds ratio. Note: Direct cross-modality comparison is inherently limited by heterogeneity in study design, patient populations, bleeding definitions, and outcome measures across included studies. Level of evidence reflects the highest quality study available for each modality in the gastric cancer bleeding context.

9. Multidisciplinary Management and Optimal Treatment Sequencing

The complexity of hemorrhagic gastric cancer—spanning acute oncologic emergencies, competing procedural modalities, and the imperative to preserve access to systemic therapy—renders a multidisciplinary team (MDT) approach not merely advisable but essential. Optimal MDT composition includes gastroenterology, interventional radiology, surgical oncology, radiation oncology, and medical oncology, with each discipline contributing expertise at distinct nodes of the treatment algorithm.

Patient performance status (ECOG PS) is the central determinant of treatment pathway selection. For patients with ECOG PS $\geq$ 3, repetitive invasive procedures carry unacceptable risk; short-course palliative radiotherapy (30 Gy/10 fractions or 6 Gy/3 fractions) represents the most pragmatic hemostatic strategy. For patients with ECOG PS 0–1 and potentially resectable disease, the recommended approach, where clinically feasible, is a two-stage strategy: hemostatic control (endoscopy or TAE) $\rightarrow$ clinical stabilization $\rightarrow$ CT restaging $\rightarrow$ radical gastrectomy, maximizing the probability of oncologic cure without exposing an acutely ill patient to the risks of emergency resection.

Key Point: *The ultimate goal of hemorrhage management in gastric cancer is not simply to stop the bleeding—it is to create a therapeutic window that enables systemic anticancer treatment, which represents the most powerful determinant of long-term survival.*

10. Limitations of Current Evidence

A critical appraisal of the evidence reviewed in this article reveals several important limitations that temper the strength of the clinical recommendations presented.

10.1. Retrospective Study Designs and Small Sample Sizes

The overwhelming majority of studies on gastric cancer-related hemorrhage are retrospective in design, predominantly single-institution series with modest sample sizes. Prospective data and randomized controlled trials specifically designed for this clinical scenario are virtually absent, with the notable exception of two prospective studies on TC-325 hemostatic powder. Retrospective designs are inherently susceptible to selection bias, referral bias, and unmeasured confounding, which may inflate reported hemostatic success rates.

10.2. Heterogeneity in Definitions of Treatment Success

Substantial heterogeneity exists across studies in the operational definitions of technical success and clinical success. In endoscopic studies, clinical success is variously defined

as absence of rebleeding within 3, 7, or 30 days. In TAE studies, it may refer to sustained hemostasis without emergency surgery. In radiotherapy studies, hemostatic response is assessed by transfusion reduction, hemoglobin stabilization, or blood transfusion-free survival. This heterogeneity renders direct cross-modality comparisons unreliable.

10.3. Variability in Radiotherapy Protocols

Palliative radiotherapy has been administered across a wide range of dose fractionation schemes—from single-fraction (6 Gy $\times$ 1) to conventional fractionation (40 Gy/20 fractions)—with corresponding BED₁₀ values spanning from approximately 9.6 Gy to 56 Gy. No head-to-head randomized comparison of different fractionation schedules has been conducted.

10.4. Absence of Randomized Controlled Trial Evidence for Most Modalities

With the exception of two RCTs evaluating TC-325 hemostatic powder, no randomized controlled trial data exist for endoscopic hemostasis modalities, TAE, palliative radiotherapy, or surgical intervention specifically in the context of gastric cancer-related bleeding. The entire evidence base for these interventions relies on observational data, which cannot exclude confounding by indication.

10.5. Selection Bias

Selection bias operates at multiple levels. Patients stable enough to undergo endoscopy, TAE, or radiotherapy are systematically healthier than those managed conservatively. Studies from high-volume tertiary centers may not reflect outcomes achievable in community settings.

10.6. Geographic Concentration

The large majority of studies originate from East Asian countries—primarily the Republic of Korea, Japan, and China—where gastric cancer epidemiology, histologic subtype distribution, treatment infrastructure, and healthcare characteristics may differ substantially from Western cohorts. The generalizability of reported outcomes to non-Asian populations should be interpreted with appropriate caution.

10.7. Implications for Future Research

These limitations highlight the urgent need for: (i) multicenter prospective registries with standardized outcome definitions; (ii) randomized controlled trials comparing endoscopic modalities; (iii) prospective dose-fractionation trials for palliative radiotherapy with BED₁₀ as the primary stratification variable; (iv) validation studies of predictive models for rebleeding in non-Asian populations; and (v) prospective evaluation of the combined endoscopy–TAE–radiotherapy sequential strategy.

11. Future Perspectives

11.1. Advances in Endoscopic Technology

The over-the-scope clip (OTSC) system employs a nitinol clip of substantially greater diameter than conventional through-the-scope clips. In non-variceal upper gastrointestinal bleeding from benign causes, a systematic review and meta-analysis by Zhong et al. (16 studies; n = 769 patients) reported a pooled technical success rate of 92.7% and clinical success rate of 89.4% [41], and a subsequent meta-analysis by Bapaye et al. (10 studies, 4 RCTs; n = 914 patients) confirmed significantly lower rebleeding rates with OTSC versus standard therapy [42]. However, the applicability of OTSC to gastric cancer-related bleeding requires critical qualification. The mechanism of OTSC—en-bloc tissue capture and compression of a discrete focal vessel—is best suited to a hemorrhage pattern with a single identifiable bleeding point in firm, fibrotic tissue. This prerequisite is frequently

absent in advanced gastric cancer, where bleeding typically arises from diffuse, extensive, friable tumor surfaces lacking a focal vessel amenable to clip-based occlusion. Published evidence for OTSC specifically in gastric cancer bleeding remains confined to isolated case reports [22,23], and OTSC should be regarded as an investigational modality in this context, applicable only to the highly selected subset with a focal accessible bleeding vessel amenable to cap loading. Additionally, EUS-guided hemostasis—involving direct targeting of dominant tumor-feeding vessels—has been reported as a rescue modality following TAE failure in advanced gastric cancer [43].

11.2. Refinement of Radiotherapy Techniques and Integration with Systemic Therapy

The application of intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) to hemostatic indications in gastric cancer remains investigational but potentially transformative. A 3D-CRT series demonstrated a hemostatic success rate of 95% with a rebleeding rate of 10.5%, outperforming most historical comparators—though isolated gastric perforations were reported [40]. Concurrent integration of hemostatic radiotherapy with anti-VEGF agents presents a nuanced challenge: ramucirumab, a standard second-line agent in advanced gastric cancer, significantly increases the risk of low-grade hemorrhagic events (RR 2.06; 95% CI, 1.85–2.29) [44], necessitating individualized risk-benefit assessment when initiating antiangiogenic therapy in patients with recent tumor bleeding. As immune checkpoint inhibitors become increasingly embedded in first-line treatment, prospective data on optimal sequencing of hemostatic interventions with immunotherapy are urgently needed.

11.3. Artificial Intelligence and Rebleeding Prediction Models

Current risk stratification for gastric cancer-related hemorrhage relies on instruments validated in benign peptic ulcer disease, creating a critical evidence gap for oncologic practice. A multicenter study applying machine learning to predict post-ESD bleeding in early gastric cancer demonstrated significantly superior discriminatory performance compared with conventional logistic regression (AUC 0.80 vs. 0.71; $p = 0.03$) [45]. Development of integrated prediction models—incorporating clinical, endoscopic, and imaging parameters—promises to enable prospective identification of patients at highest risk of rebleeding, facilitating pre-emptive escalation to definitive hemostatic therapy and optimizing the sequencing of subsequent systemic treatment.

12. Conclusions

Massive hemorrhage complicating gastric cancer can be fatal within 24 h of onset, and the success or failure of hemostatic intervention exerts a measurable influence on patient survival. Hemostatic control must be recognized not as a terminal therapeutic act, but as a gateway to oncologic treatment—the foundational prerequisite that enables chemotherapy or curative surgery to exert their survival benefit.

This review distills the available evidence into four guiding clinical principles. First, endoscopic hemostasis is the standard first-line treatment in hemodynamically stable patients; failure mandates prompt escalation to TAE or palliative radiotherapy, with surgical rescue available when all other options are exhausted. Second, transfusion of ≥ 5 packed RBC units is the singular independent predictor of early rebleeding; in such patients, adjunctive palliative radiotherapy ($\text{BED}_{10} \geq 39$ Gy) should be proactively planned even after initially successful endoscopic hemostasis. Third, rapid transition to systemic chemotherapy following successful hemostasis is the most powerful modifiable determinant of survival, and CT restaging for resectability should be performed in all patients achieving hemodynamic stability. Fourth, all clinical decisions should be made within an MDT framework, integrat-

ing performance status, disease extent, prior treatment history, and patient preferences to ensure individualized, evidence-informed care.

The current evidence base is constrained by the predominance of retrospective, single-institution studies and the absence of validated, tumor-specific hemorrhage risk stratification tools. Multicenter prospective trials and randomized controlled studies specifically designed for gastric cancer-related bleeding are urgently needed to establish the evidence foundation for future guideline development.

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