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Review

Impact of Anastomotic Leakage on Overall and Disease-free Survival After Surgery for Gastric Carcinoma: A Systematic Review

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Abstract. *Background/Aim: Gastric cancer is the fifth most frequently diagnosed cancer and the second most common cause of cancer-related death. The only potentially curative treatment is surgical resection, which is associated with potentially severe complications, such as anastomotic leakage. The aim of this systematic review was to evaluate the relationship between anastomotic leakage and overall and disease-free survival after surgery for gastric cancer. Materials and Methods: A systematic literature search was performed and 7 articles published between 2010 and 2019 were included, including a total of 7,167 patients. Results: Among the included studies the frequency of anastomotic leakage ranged from 6 to 41%. Patients affected by anastomotic leakage had an overall survival ranging between 4.1 and 97.6 months, whereas patients who did not experience anastomotic leakage had an overall survival between 23 and 109.5 months. Conclusion: Closer follow-up or even more aggressive oncological therapy may be considered for patients affected by anastomotic leakage after surgery for gastric cancer.*

Gastric cancer is the fifth most frequently diagnosed cancer and the second most common cause of cancer-related death (1-2). In the world, annually, more than one million diagnoses of gastric cancer are made and the incidence of gastric cancer is highly dependent on region and culture (2). The cumulative risk of developing gastric cancer from birth to age 74 is higher in males, amounting for 1.87% against a cumulative risk of 0.79% in females worldwide.

The management of patients with gastric cancer is interdisciplinary, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. Nowadays, surgery remains the primary treatment option for patients with resectable tumors (2, 3).

For patients with cT2 or even more advanced gastric tumors, perioperative chemotherapy and preoperative chemoradiation (category 2B) should always be considered, even if surgical resection with negative margins (R0) remains the most important step of the treatment (3).

However, gastric cancer surgery may be associated with several complications. The overall complication rate after radical gastrectomy for gastric cancer is 18.7%. The most common complication is anastomotic leakage (AL), which affects up to 3.4% of patients (3, 4).

The long-term consequences of AL following gastric cancer surgery are still debating. The aim of our work was to analyse the impact of AL on disease-free-survival (DFS) and overall survival (OS) in patients who underwent gastrectomy for cancer, through a careful analysis of the results currently available in the literature.

Patients and Methods

Search strategies. We conducted a systematic search in PubMed, Embase, Cochrane Library, CILEA Archive, BMJ Clinical Evidence and Up ToDate databases with the following search terms: "cancer" AND "gastric" (or "stomach") AND "anastomotic leakage" (or

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Key Words: Gastric cancer, disease-free survival, overall survival, anastomotic leakage, review.

Table I. *Characteristics of the included studies with quality assessment (NOS score).*

First author year	Study type	Country	Histology	Study period	Patients, n	AL (%)	Age Years median	Gender M/F	NOS score
Tsusjimoto *et al*. (10) 2008	RCS	Japan	AC	1986-2005	1332	48	61.2	905/427	7
Sierzega *et al*. (11) 2010	RCS	Poland	AC	1999-2004	690	41	63.7	458/232	7
Han Mo Yoo *et al*. (12) 2011	RCS	Korea	AC	2000-2005	478	32 (6.7%)	58	326/152	9
Kim *et al*. (13) 2015	RCS	Korea	AC	2003-2012	3.827	72 (1.88%)		2,602/1,225	8
Samples *et al*. (14) 2015	RCS	USA	AC	2004-2012	102	6	62.9	74/28	8
Andreou *et al*. (15) 2016	RCS	Germany	AC S	2005-2012	471	41	65	353/118	9
Barchi *et al*. (16) 2019	RCS	Brazil	AC	2009-2017	258	15 (5.8%)	62.3	180/78	9

RCS: Retrospective cohort study; AC: adenocarcinoma; S: squamous; AL: anastomotic leakage.

fistula or dehiscence) AND “overall survival “ AND “disease-free survival ” AND “recurrence” AND "long-term-results".

We also scanned all the reference lists to identify other relevant studies. Unpublished reports were not considered eligible.

Compliance with ethical standards. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study selection. Inclusion criteria were: 1) articles written in English and published between January 1998 and June 2019. 2) Open or minimally invasive surgery with curative intent (with histological confirmation of R0 status). 3) Cases of gastric adenocarcinoma and/or gastroesophageal adenocarcinoma type III according to Siewert classification (5). 4) Studies mentioning overall survival and/or disease-free survival.

Exclusion criteria were: 1) treatment for disease recurrence; 2) case report; 3) letter to the Editor; 4) Review.

Data extraction and quality assessment. Two authors (GM, MC) independently screened the articles by title, abstract and keywords, and then selected and analysed the relevant articles. Any disagreement was resolved by discussion with the senior author (PA).

PRISMA statement guidelines for conducting and reporting systematic reviews were followed (6).

The research protocol was registered at the International Prospective Register of Systematic Reviews with the following registration number: CRD42019120781 (6). The Newcastle-Ottawa Scale (NOS) was used for quality assessment (7). Cochrane Collaboration guidelines were followed (8). Three broad perspectives were used to judge a study evaluating the selection of the study groups, comparability, ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively (7, 8). Results of quality assessment scale (7) are reported in Table I. The study was designed and reported according to the STROCSS criteria (9).

Results

The literature search yielded 135,194 items; 135,001 were not considered suitable for abstract or integral reading, including duplicates removal. Then, 193 titles and abstracts were reviewed (Figure 1). A total of 180 papers were excluded because they did not match our inclusion criteria. Finally, only 13 articles were selected for full-text review and of these, six more were excluded for the following reasons: Five because they did not report OS or DFS rates in patients with occurrence of anastomotic leakage and one because it did not report AL rates. There was no disagreement regarding eligibility of full-text articles.

A total of seven articles fulfilled the selection criteria and were included in this systematic review (10-16). This pool of articles consisted of seven retrospective reports. Characteristics of the included studies are presented in Table I. Table II shows the outcomes.

A total of 7,167 adult patients who underwent surgery for gastric and GEJ cancer (type III according to Siewert Classification) were included.

Tsujimoto *et al*. (10) have evaluated the influence of postoperative infection on long-term survival after potentially curative gastrectomy in 1,332 patients. Two groups of patients were considered: 141 patients composed the first group, who had postoperative complications (10.6%). The second group, without postoperative complications, included the other 1,191 patients. The OS of patients with stage II gastric cancer was 65.6% (no postoperative complications) *versus* 49.7% if they experienced postoperative complications (p=0.04). OS was 41.2% for patients with stage III gastric cancer but if they experienced postoperative complications it dropped to 20.6%, (p=0.002). Multivariate analysis demonstrated that AL was significantly associated with cancer-specific survival (10).

Sierzega *et al*. (11) included 699 patients of whom 41 were affected by AL (5.8%). The group with AL had 5-years DFS of 11 months. The group without complications had a 5-year DFS of 19 months (p=0.021). The OS was 4.1 months and 23 months, respectively (p=0.001).

Han Mo Yoo *et al*. (12) included 478 patients. AL was found in 35 patients (6.7%). In the group of patients affected by leakage, the overall mean survival was significantly

The STROCSS Guideline		
Item no.	**Item description**	Page Number
1	Title: The words "cohort" and the area of focus should appear in the title (*e.g.* disease, exposure/intervention or outcome). Whether the study is retrospective or prospective should also be stated.	1
2a	Abstract - Introduction: The background and scientific rationale for the research question.	2-3
2b	Abstract - Methods: Describe the study design (cohort design, retrospective or prospective, single or multi-centre, etc), what was done to each group, how, when was it done and by whom.	2-3
2c	Abstract - Results: What was found. Give the results for the main outcomes.	2-3
2d	Abstract - Conclusion: What have we learned and what does it mean. Where should future research go.	2-3
3	Explain the scientific background and rationale for the cohort study. What are objectives, research questions and the hypotheses.	3-4
4a	Registration and ethics: State the research registry number in accordance with the declaration of Helsinki - "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject" (this can be obtained from; ResearchRegistry.com or ClinicalTrials.gov or ISRCTN). Even retrospective studies should be registered prior to submission.	-
4b	Ethical Approval: State whether ethical approval was needed and if so, what the relevant judgement reference from the IRB or local ethics committee was? If ethical approval was not needed, state why.	-
4c	Protocol: Was a research protocol developed apriori? Where can it be accessed. Was it published in a journal e.g. IJS Protocols, BMJ Open, etc, if so, provide the reference.	-
5a	Study design - State the research is a cohort study and whether prospective or retrospective in design, whether single or multi-centre.	4
5b	Setting: Describe the setting(s)and nature of the institution in which the patient was managed; academic, community or private practice setting? Location(s), and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	4-5
5c	Cohort Groups: State the number of groups in the study. What interventions will each group receive?	-
5d	Sub-group–Analysis: Any planned sub-group analyses are specified / Describe any methods used to examine subgroups and interactions.	-
6a	Participants: State any eligibility (inclusion/exclusion) criteria and the sources and methods of selection of participants. Describe length and methods of follow-up.	3-4
6b	Recruitment: State the methods of how patients or participants were recruited to each group, over what time periods.	3-4
6c	Sample size calculation: Whether there was calculation of margin of error or a prior analysis to determine study population, or mention of how appropriate study sample was determined.	3-4
7a	Pre-intervention considerations - e.g. Patient optimisation: measures taken prior to surgery or other intervention e.g. treating hypothermia/hypovolaemia/hypotension in burns patients, ICU care for sepsis, dealing with anticoagulation/other medications and so on.	-
7b	Types of intervention(s) deployed: To include reasoning behind treatment offered (pharmacological, surgical, physiotherapy, psychological, preventive) and concurrent treatments (antibiotics, analgesia, anti-emetics, nil by mouth, VTE prophylaxis, etc). Medical devices should have manufacturer and model specifically mentioned.	-
7c	Peri-intervention considerations: Administration of intervention (what, where, when and how was it done, including details for surgery; anaesthesia, patient position, use of tourniquet and other relevant equipment, preparation used, sutures, devices, surgical stage (1 or 2 stage, etc) and operative time. Pharmacological therapies should include formulation, dosage, strength, route and duration). Authors are encouraged to use figures, diagrams, photos, video and other multimedia to explain their intervention.	-
7d	Who performed the procedure(s): Operator experience for each group (position on the learning curve for the technique if established, specialisation and prior relevant training).	-
7e	Quality control: What measures were taken to reduce inter or intra-operator variation. What measures were taken to ensure quality and consistency in the delivery of the intervention e.g. independent observers, lymph node counts, etc.	-
7f	Post-intervention considerations - e.g. post-operative instructions and place of care: Important follow-up measures - diagnostic and other test results. Future surveillance requirements - e.g. imaging surveillance of endovascular aneurysm repair (EVAR) or clinical exam/ultrasound of regional lymph nodes for skin cancer.	-
8	Outcomes: What primary and secondary (if any) outcomes will be assessed and how are they defined. Definitions should be clear and precise. Appropriate references to validation of outcome measures used should be provided if they exist.	3-4
9	Statistical methods: Clearly outlined statistical tests used to compare the outcomes between an intervention group and a comparison group, state whether pre-existing differences and known confounders were controlled. The statistical package used should be mentioned.	3-4
10a	Participants recruited with a flow diagram: Report numbers involved in each group and use a flow diagram to show recruitment, non-participation, cross-over, withdrawal from the study with reasons.	3-4
10b	Comparison between groups including a table: Provide a table comparing the demographic, clinical/prognostic features (co-morbidities, tumour staging, smoking status, etc) and relevant socioeconomic characteristics of each group and whether numerical differences are significant (using p-values and/or confidence intervals as appropriate). Were the groups matched and if so, how.	-
10c	Changes: Any changes in the interventions during the course of the study (how has it evolved, been altered or tinkered with, what learning occurred, etc) together with rationale and a diagram if appropriate.	-
	Degree of novelty for a surgical technique/device should be mentioned and a comment on learning curves should be made for new techniques/devices.	
11a	Outcomes and follow-up: Clinician assessed and patient-reported outcomes (when appropriate) should be stated for each group (size of effect with raw numbers and percentages) with inclusion of the time periods at which assessed. Relevant photographs/radiological images should be provided e.g. 12-month follow-up.Make it clear which confounders were adjusted for and which were not.	-
11b	Intervention adherence/compliance and tolerability: How was this assessed. Describe loss to follow-up (express as a percentage and a fraction) or cross-over between group and any explanations for them.	-
11c	Complications and adverse or unanticipated events: Describe in detail and ideally categorise in accordance with the Clavien-Dindo Classification. How they were prevented, mitigated, diagnosed and managed. Blood loss, wound complications, re-exploration/revision surgery, 30-day post-op and long-term morbidity/mortality may need to be specified.	-
12	Summarise key results.	4-5
13	Discussion of the relevance of the findings and rationale for conclusions: Relevant literature, implications for clinical practice guidelines, how have the indications for a new technique/device been refined and how do outcomes compare with established therapies and the prevailing gold standard should one exist and any relevant hypothesis generation. The rationale for any conclusions.	4-5
14	Strengths and limitations of the study.	4
15	State what needs to be done next, further research with what study design(s).	5
16	State the key conclusions from the study and key directions for future research.	5
17a	State any conflicts of interest.	5
17b	State any sources of funding.	-

Figure 1. *The STROCSS Guideline*.

lower: 30.5 *versus* 96.2 months ($p<0.001$). AL was an independent factor predictive for overall survival (HR=3.58, 95%CI=2.29-5.59).

Kim *et al*. (13) included a total of 3,827 patients. They reported an AL rate of 1.88%. They did not report the OS, and they showed a median DFS of 97.6 months in patients with AL and a median DFS of 109.5 months in patients, who did not experience AL ($p=0.076$).

Samples *et al*. (14), collected data of 102 patients. Six ALs occurred (5.8%). The 5-year DFS was not reported.

Andreou *et al*. (15) collected data from 471 patients. 41 patients were affected by AL (8.7%), with a 5-year overall

Table II. *Primary outcomes of each included study.*

Authors, year (Ref)	Follow-up duration, months (range)	AL, n	5-Year DFS (%)		OS (mo)	
			AL	NL	AL	NL
Tsusjimoto *et al*. (10) 2008	68.5 (3-211)	48 (3.6%)	NR	NR	NR *0.0015	NR
Sierzega *et al*. (11) 2010	34 (5-501)	41 (5.9%)	11 mo *0.021	19 mo	4.1 mo *0.001	23 mo
Yoo *et al*. (12) 2011	62.5 mo	32 (6.7%)	28.4 *0.001	97.2 *0.001	30.5 mo	96.2 mo
Kim *et al*. (13) 2015	58.5 (0-136)	72 (1.88%)	97.6 *0.076	109.5	NR	NR
Samples *et al*. (14) 2015	20.3 mo	6 (5.8%)	NR	NR		Median OS 70.3 *0.17
Andreaou *et al*. (15) 2016	35 (1-101)	41 (8.7%)	35% *0.005	58%	39% (n=41) *0.005	61% (n=430)
Barchi *et al*. (16) 2019	25.5 (1-102)	15 (5.8%)	NR	NR	50 mo *0.013	100 mo

AL: Anastomotic leakage; DFS: disease-free survival; OS: overall survival; NL: non anastomotic leakage; NR: non reported; mo: months; *p-value reported in the reference articles; n=number of patients.

survival rate of 35% *versus* not AL of 58% (p=0.005). OS in patients with AL was 39% *versus* 61% in those without AL (p=0.005).

Barchi *et al*. (16) enrolled 258 patients. They had 15 patients with AL (5.8%). In this manuscript the 5-year DFS was not reported. The OS was 50 months in patients with AL *versus* 100 months in patients without AL.

Discussion

The aim of our work was to analyse the impact of AL on DFS and OS after gastric cancer surgery. The relationship between AL and long-term results after surgery for gastric cancer is still the subject of debate. Our group has recently published a review regarding the relationship between AL and oesophageal cancer, showing how, with a proper literature analysis, is it possible to highlight the relationship between AL and survival (17). A similar investigation was performed on colorectal surgery, concluding that AL after proctectomy for cancer is associated with worse long-term DFS and overall survival (18).

Beecher *et al*. (19) have demonstrated in their review how surgical trauma, inflammatory response, intraoperative tumor manipulation, growth factors released during the procedure and tumor growth have a significant impact on OS and recurrence rates. Surgery can indeed bring to suppression cell-mediated immunity and diffusion of malignant cells into the bloodstream, therefore, increasing the metastatic potential. In our research, five articles showed that AL had a statistically significant impact on the OS and DFS (10-12, 15, 16), and two articles written by Kim *et al*. and Samples *et al*. did not find any statistically significant relationship (13, 14).

The studies showing that AL had a statistically significant impact on OS and DFS included 3,238 patients, whereas the study that did not found any correlation between AL and long-term results (13, 14) included a total of 3,929 patients. In absolute numbers, articles showing no correlation between AL and worse long-term outcomes have a higher number of enrolled patients. However, the studies showing a significant correlation between AL and survival included more patients with AL: 273 patients had AL (8.4%, range=5.8-10.6%) in this group *versus* 78 patients (1.9%, range=1.88-5.8%) in the articles not showing any significant relationship. The smaller number of patients with AL may limit the statistical power of studies not showing any correlation.

Indeed, a global analysis of the data shows that there is a negative trend in long-term outcomes (worse DFS and worse OS) in patients with AL.

Tsujimoto *et al*. (10), did not report OS as months of survival, but in the multivariate analysis they demonstrated the negative impact of AL on OS (p=0.0015). Moreover, they analysed the correlation between AL and cancer-specific survival finding a statistically significant correlation (p=0.0358).

Sierzega *et al*. (11) demonstrated how AL has negative effects on OS and DFS. They showed that patients with AL had an OS of 4.1 months *versus* 23 months for patients who did not have AL (p=0.001). Regarding DFS, they have shown that patients with AL had worse overall survival: 11 months compared to 19 months in patients without AL (p=0.021). In this study, the factors predisposing to AL were also analysed; they demonstrated that poor performance status had the greatest impact as a predictive factor of AL.

Yoo *et al*. (12) demonstrated that AL has a negative impact on OS and DFS, in a multivariate analysis (p<0.001).

They also identified AL as one of the causes of cancer-related death (32.2 *vs*. 99.5 months; $p<0.001$), and recognized poor performance status as the most important factor predisposing to AL.

Andreau *et al*. (15) showed that AL is a significantly predictor of worse OS ($p=0.037$) and DFS ($p=0.004$). In their analysis, AL turned out to be an unfavourable factor independently from tumor stage and biology, and in the multivariate analysis for factors associated with tumor recurrence, AL was an independent predictor of tumor recurrence ($p=0.002$).

Barchi *et al*. (16) demonstrated that OS is statistically worse in patients with AL than in non-AL patients. They reported 15 fistulas in 258 patients operated for gastric cancer, with decreased OS in patients with AL compared to non-AL (50 months and 100 months, respectively). Barchi *et al*. recognized the type of surgery as a major cause of AL (total *vs*. completion gastrectomy).

Kim *et al*. (13) analysed a cohort of 3827 patients. They had 72 fistulas, 1.88% of the total number of included patients. They showed that patients with leakage and without leakage did not differ significantly in terms of DFS ($p=0.076$). Their statistics also showed that the AL was not associated with cancer-related death.

Samples *et al*. (14), in their analysis, showed that there is no correlation between AL and worse OS.

During the selection of the articles, some were excluded because they did not strictly respect the inclusion criteria. They did not specifically investigate the relationship between AL and worse long-term survival, but they analysed the negative impact of AL on general complications, pathological stage, surgical technique, inflammation, and the long-term survival (20-27). The impact of AL on the prognosis of several cancers is still debated (28-31).

All the included studies were retrospective, carrying an intrinsic risk of selection bias, including heterogeneity linked to the changes in clinical practice, technology, surgical and chemoradiotherapy protocols. Indeed, changes in adjuvant chemotherapy practice may have included some selection bias, with patients treated in the most recent years showing better oncological outcomes due to more effective protocols. The definition of AL, reported in 5 out of 7 articles (11-16), appeared to be different among the studies, because it was based on different clinical parameters. In all the articles, AL, when recognized, was investigated radiologically. The different classification used for the gravity of AL evaluation could be a potential source of bias. Only 2 articles reported the Clavien-Dindo classification: Barchi *et al*. (16) reported 3 AL of grade I-II and 12 AL of grade III-V; Samples *et al*. (14) reported 6 ALs of grade III. Moreover, none of the articles stratified the risk based on tumor staging except for Barchi *et al*. (16).

Conclusion

The majority of reviewed studies showed an association between AL and DFS and OS. Closer follow up or an even more aggressive oncologic therapy may be considered for patients affected by postoperative anastomotic leakage.

Conflicts of Interest

None of the Authors had any conflicts of interest to declare.

Authors' Contributions

Paolo Aurello gave substantial contribution in the design of the work, drafting the work, final approval of the version to be published. Matteo Cinquepalmi, Niccolò Petrucciani and Giovanni Moschetta gave substantial contribution in the acquisition, analysis and interpretation of data for the work, drafting the work and final approval of the version to be published. Laura Antolino, Federica Felli, Diego Giulitti, Giuseppe Nigri, Francesco D'Angelo, Stefano Valabrega and Giovanni Ramacciato gave substantial contribution in critically revising the article for important intellectual content and final approval of the version to be published. All Authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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