ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:
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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

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MEDICAL SCHOOL

MASTER THESIS

CURRENT EVIDENCE ON LAPAROSCOPIC VERSUS OPEN RESECTION FOR GASTRIC STROMAL TUMORS (REVIEW)

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Περίληψη

Παρότι η χρήση της λαπαροσκοπικής χειρουργικής αυξάνει ολοένα, υπάρχουν ακόμα επιφυλάξεις για την εφαρμογή της σε κακοήθειες. Οι στρωματικοί όγκοι του γαστρεντερικού (GISTs) είναι λιγότερο απαιτητικοί σε λεμφαδενεκτομές, δεδομένο που σημαίνει ότι ίσως οι λαπαροσκοπικές εκτομές να έχουν ένα σαφές και ξεκάθαρο πλεονέκτημα, όταν συγκρίνονται με τις ανοικτές επεμβάσεις. Με βάση την τρέχουσα βιβλιογραφία, δεν υπάρχουν τυχαιοποιημένες μελέτες που να συγκρίνουν τις λαπαροσκοπικές με τις ανοιχτές χειρουργικές εξαιρέσεις GISTs. Η παρούσα μελέτη είχε ώς στόχο να εξετάσει την τρέχουσα βιβλιογραφία με όρους συστηματικής ανασκόπησης (Systematic Review). Διενεργήθηκε συστηματική αναζήτηση της βιβλιογραφίας ανεξάρτητα από δύο συγγραφείς, σε τρεις ανεξάρτητες βάσεις δεδομένων, χρησιμοποιώντας συγκεκριμένους όρους αναζήτησης. Διερευνήθηκαν οι τίτλοι, οι περιλήψεις, τα πλήρη κείμενα και οι αναφορές των σχετικών άρθρων, προκειμένου να γίνει επιλογή των μελετών που τελικά συμπεριλήφθηκαν στην ανασκόπηση. Τα δεδομένα αντλήθηκαν με βάση προσυμφωνημένη φόρμα. Οι μελέτες αξιολογήθηκαν με βάση τα τροποποιημένα κριτήρια MINORS. Συνολικά, συμπεριλήφθηκαν δέκα (10) μελέτες. Οι περισσότερες ανέφεραν σημαντικά βελτιωμένα περιεγχειρητικά αποτελέσματα (διάρκεια επέμβασης, απώλεια αίματος, διάρκεια παραμονής στο νοσοκομείο) για τη λαπαροσκοπική προσέγγιση. Μόνο τέσσερις μελέτες ανέφεραν μακροχρόνια αποτελέσματα και ευρήματα που ήταν αντικρουόμενα, με κάποιες μελέτες να μη δείχνουν στατιστικά σημαντικές διαφορές, μία να αναφέρει καλύτερα και μία χειρότερα αποτελέσματα, ως προς την ελεύθερη νόσου επιβίωση και ως προς τη συνολική επιβίωση, στη λαπαροσκοπική ομάδα. Τρεις μελέτες έδειχναν ποιοτικά καλές, οι δύο εκ των οποίων δεν έδειξαν στατιστικά σημαντικές διαφορές στα μακροχρόνια αποτελέσματα, ενώ η τρίτη έδειξε στατιστικά σημαντικό πλεονέκτημα στην ομάδα ανοικτής προσπέλασης. Ενώ υπάρχει σαφές πλεονέκτημα στην λαπαροσκοπική χειρουργική αντιμετώπιση των ασθενών με GIST σχετικά με τα περιεγχειρητικά αποτελέσματα, υπάρχει αρκετή ασάφεια σχετικά με τα μακροχρόνια ογκολογικά αποτελέσματα. Η έλλειψη τυχαιοποιημένων μελετών, όπως επίσης και η φτωχή αναφορά αναδρομικών μελετών, περιορίζουν το ποσό των αποδείξεων που είναι διαθέσιμες προς το παρόν. Η λαπαροσκοπική χειρουργική αντιμετώπιση των GISTs είναι σίγουρα ασφαλής, εφικτή και αποτελεσματική. Παρόλα αυτά, απαιτούνται επιπλέον μελέτες για να επιβεβαιωθεί η υπεροχή της σε σχέση με την ανοιχτή προσέγγιση.

Λέξεις Κλειδιά:

Στρωματικοί όγκοι γαστρεντερικού, λαπαροσκόπηση, λαπαροσκοπική χειρουργική, ελάχιστα επεμβατική χειρουργική, υποτροπή, επιβίωση.

Abstract

Although the use of laparoscopic surgery is increasing, controversy still surrounds its application for malignant conditions. Gastrointestinal stromal tumours (GISTs) are less demanding in terms of lymphadenectomy, meaning that laparoscopic resection might have a more defined benefit when compared with open resection. To the best of our knowledge, no randomized study exists that compares the laparoscopic and open resection of GISTs. The current study aimed to examine the relevant literature by means of a systematic review. A systematic literature search was performed individually by two authors, in which three independent databases were searched using specific search-terms. Titles, abstracts and full texts were screened, as well as references to relevant articles, in order to comprise a comprehensive list of studies. Data were extracted using a detailed pre-agreed spreadsheet. Studies were evaluated according to the modified MINORS criteria. A total of 10 studies were included in the present review, yielding a total of 14 entries. The majority of studies reported significantly improved perioperative outcomes for the laparoscopic approach, including improved duration of operation, blood loss and length of hospital stay. Only four studies reported long-term outcomes and findings that were controversial, with some studies detecting no statistically significant differences, one reporting improved and one reporting worse disease-free and overall survival for the laparoscopic group. Three studies were deemed to be good quality, two of which had not reported significantly different long-term outcomes, while the third had reported significantly improved outcomes in the open resection group. While there is a clear benefit for performing laparoscopic surgery in patients with GIST with regards to perioperative outcomes, when it comes to long-term oncological outcomes, uncertainty over its application remains. The lack of randomized trials, as well as the poor reporting of retrospective studies, limits the amount of evidence that is currently available. Laparoscopic surgery for GIST is certainly safe, feasible and likely cost-effective; however, further studies are required to inform on whether this technique is superior to open resection.

Key Words:

Gastrointestinal stromal tumours, laparoscopy, laparoscopic surgery, minimal invasive surgery, recurrence, survival.

Ευχαριστίες

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Contents:

1. Introduction

The laparoscopic approach for abdominal surgery has been increasingly applied, becoming the gold standard for numerous surgical procedures, including appendicectomy (1), sigmoidectomy for diverticular disease (2), left lateral hepatectomy for benign lesions (3,4) and bariatric roux-en-y gastrectomy (5). However, previous studies on this technique have been variable regarding its surgical application for malignant conditions. Although this approach is beneficial in terms of postoperative recovery, early postoperative quality of life and postoperative complications (6), other issues arise when it comes to oncologic resections, such as achievement of R0 resection, disease free survival (DFS) and overall survival (OS), where contradictory evidence questions the value of laparoscopic surgery (7,8). Postulated causes include surgeons performing laparoscopic resections while still in training, along with a lack of tactile feedback that might lead to increased R1 resections. Other concerns include the dissemination of cancer cells due to pneumoperitoneum (9), and in gastric surgery specifically, the inability to perform adequately extensive lymphadenectomy, which is crucial for gastric cancer oncological outcomes (8).

Gastrointestinal stromal tumours (GISTs) are malignant lesions of the gastrointestinal tract, arising from interstitial Cajal cells. Positive long-term outcomes in patients with GISTs rely on the success of surgical resection. Contrary to gastric adenocarcinoma, extensive lymphadenectomy does not appear to be considered as important for GISTs (10). This observation, along with the fact that GISTs are usually well-localized tumours, presents advantages for laparoscopic resection. Several studies have demonstrated the safety and efficacy of GIST laparoscopic resection (11). However, almost all of these are retrospective studies, and although short-term outcomes have been extensively presented and discussed, long-term oncological outcomes have not been adequately reported. Current findings have been incorporated into respective guidelines, with conclusions stating that basic oncologic principles should be adhered to, including complete resection and the avoidance of rupture (12,13). Therefore, laparoscopic surgery may be reserved for smaller tumours (12, and for tumours of the anterior wall of the stomach (13).

The present study aimed to examine current evidence regarding the oncological outcomes of laparoscopic resection in comparison with open resection performed in patients with GISTs. To achieve these aims, a systematic review was performed, in which relevant studies were critically evaluated.

2. Literature search

Two authors of the current study separately carried out the literature search, study screening and selection, data extraction and study evaluation. Disagreements that arose were settled by a third author. The literature search was conducted across three independent databases, including PubMed, Library, Information Science & Technology Abstracts (EBSCO) and the Library of Congress. Two groups of search terms were used. The first group included one of the following terms: 'Minimal', 'minimally', 'MIS', 'laparoscopic' and 'laparoscopically'. The second group included one of the following terms: 'GIST', 'stroma', 'stromal', 'stromatic', 'mesenchymal' and 'mesenchymatic'. Search terms regarding the anatomical area of the stomach were not used in the present literature search due to the large variability of relevant descriptors. Manual screening was performed in place of this. All possible combinations of one term per group were searched for in the title and/or abstract of studies. The search was limited to articles published from 2016 onwards to cover the last 5 years to date. Only those published in English, and only the studies reporting direct comparisons between laparoscopic resection and open surgery were included. The exclusion criteria were as follows: Unavailability of full text, tumour size limitations and secondary studies, such as reviews and meta-analyses. Upon the initial literature search and following the removal of duplicates, titles and abstracts were screened for relevance. Full texts were retrieved for those that were deemed relevant. References were screened for relevant articles that were potentially not detected through the initial literature search, and respective full texts were additionally retrieved. Finally, full texts were screened and selected for inclusion in the present study.

3. Data extraction

Data were extracted using a pre-agreed pro forma spreadsheet. Data included: First author, year of publication, studied time period, type of design (prospective vs. retrospective; cohort vs. subgroup vs. propensity score matching), total number of patients, number of patients per group (laparoscopic vs. open), sex (as a percentage of males per group), age (as the median age in years per group), tumour size (as the median maximum diameter in cm per group), conversion rate, R0 achievement (as the rate per group), duration of operation (as the median duration in min per group), intraoperative blood loss (as median blood loss in ml per group), length of hospital stay [as median length of stay (LoS) in days per group], complication rate [as the percentage of patients that developed grade III or IV complications according to the Dindo-Clavien classification (14), per group], duration of follow-up (as the median follow-up in months per group), recurrence rate (as the percentage per group), DFS (for studies that reported 100% R0 resection; recorded as median

survival in months per group), 5-year recurrence free survival (for studies that reported 100% R0 resection; recorded as percentage per group), mortality (as defined in each study; recorded as the percentage per group), OS (as the median survival in months per group) and 5-year survival (as the percentage per group).

The evaluation of included studies was performed according to modified MINORS criteria (15). Plain descriptive statistics were implemented to group studies in quartiles according to overall grade.

4. Literature search results and patient demographics

The initial literature search yielded 483 papers, of which the titles and abstracts of 446 articles were screened for relevance following the removal of duplicates. A total of 22 full texts were retrieved, with 10 studies put forward for inclusion (16-25). A full cohort was provided in three studies, where propensity score matched analysis was performed, meaning that these studies yielded two entries each (19,23,24). One study presented two subgroup analyses, contributing a total of two entries (20). Consequently, 14 entries were analysed. Fig. 1 presents the flow chart of article selection, providing further details for the articles that were excluded. As predicted, there were no randomized studies.

Table I presents the design characteristics of the included entries, as well as the main epidemiological parameters. Study sample size ranged from 74 to 426 patients in total. Inclusion of the male sex ranged from 26.05 to 54% for the laparoscopic groups, and from 18.69 to 62% for the open resection groups. Median age ranged from 55 to 66 years in the laparoscopic groups and from 57 to 70 years in the open resection groups. None of the above was reported to be statistically significant. Conversion rate was not reported in four entries deriving from two studies (23,24) and was only 8% in the study performed in the USA (25). Furthermore, the conversion rate was 3.07% in one study (17) and 0% in the remaining studies.

5. Perioperative data

Table II presents perioperative data. Five entries did not report data on the completeness of resection (16,20,24). Mazer *et al* (25) reported an R0 rate of 95.83% in the open resection group (which comprised one patient). However, R0 rate was 100% in the respective laparoscopic group as well as in all other studies that reported this outcome. Median duration varied greatly from 87 to 125 min in the laparoscopic groups, and from 95 to ~700 min in the open resection groups. Nine entries reported a shorter median duration of operation for the laparoscopic approach, all of which were statistically significant. One entry reported identical median durations, while three entries

reported shorter median operative times in the open resection group, with only one of these reaching statistical significance. Four entries did not include data on intraoperative blood loss. The remaining entries presented significantly less intraoperative blood loss in the respective laparoscopic groups. One entry did not report on LoS. The remaining entries reported significantly shorter hospitalization times in the respective laparoscopic groups. Median LoS in laparoscopic groups ranged from 3 to 10 days, while the open resection group ranged from 6 to 15 days. Four entries did not report on postoperative complications, and the remaining 10 did not demonstrate statistical significance.

The duration of follow-up was reported in 11 entries, ranging from 32 to 64 months in the laparoscopic groups, and 25 to 67 months in the open resection groups. No significant differences were reported in terms of recurrence rate. Only four entries reported on DFS, two of which did not detect any significant differences (19,22). Furthermore, one entry reported a significantly longer DFS in the laparoscopic group (19), wheras another entry reported the opposite (24). Similar results were reported in OS, with two studies reporting insignificant differences (17,19), one in favour of the laparoscopic approach (19) and one in favour of the open resection approach (24). Five entries presented the 5-year recurrence-free survival rate; however, no statistically significant differences were detected. Similarly, six entries reported mortality rate, again without any significant differences. Finally, five studies reported on the 5-year survival rate, demonstrating no significant difference between the two groups. The latter ranged from 93.1 to 100% in the laparoscopic groups, and from 85.9 to 98.75% in the open resection groups. Table III presents long-term outcomes in detail.

6. Objective evaluation

All 10 studies were evaluated and scored according to the modified MINORS criteria, which produces an overall score from 0 to 18. The lowest score awarded to a study was 5, and the highest awarded study score was 15. When the full scoring spectrum was divided in quartiles, the first quartile included one study (25). The remaining three quartiles included three studies each. Three studies would be included in the top quartile with scores 14 (21), 15 (22) and 15 (24), respectively. Table IV presents this evaluation in further detail. Regarding controversial findings on perioperative data, all three top-quartile studies had reported statistical significance in favour of the laparoscopic approach. The study that had reported significantly improved findings in the open resection group received a grade of 12 and was thus included in the next quartile. Regarding discrepancies in long-term outcomes, two of the top quartile studies had detected no statistically significant differences, while the third study of the top quartile, which conducted a propensity score matched analysis, reported significantly improved DFS and OS in the open resection group (24). Furthermore, the

study that reported significantly improved DFS and OS for the laparoscopic group was allocated a score of 12 and had the largest sample size (426 patients) (19). However, in the same study, when propensity score matching was implemented, statistical significance was lost. In terms of scoring, a lack of reporting on the number of patients lost to follow up was a consistent reason for lost points; none of the included studies mentioned a relevant number. The second most common reason for lost points was study design, since only one study was prospective.

7. Historical and current topics

Since the first publication of laparoscopic GIST resection (26), ~30 years have passed, during which a marked number of studies have been published. However, questions remain regarding other indications for surgery. The early focus of research was the feasibility and safety of laparoscopic GIST resection. Although studies of cohorts within the previous decade demonstrated encouraging results, the evidence for feasibility and safety was sparse, with specific tumour features, such as size and location, appearing to mitigate reported advantages (27). This was attributed to performance bias, as surgeons were still learning how to conduct this procedure. A large multicentre study by Piessen *et al* (28) in 2015 provided a sound confirmation regarding the feasibility and safety of laparoscopic GIST resection, even for tumours that were >8 cm. Another unaddressed issue that required reliable clarification was whether laparoscopic resection demonstrated oncological inferiority compared with open resection. Recent studies have reported minimally invasive resections of malignant lesions, where disadvantages were identified over the open resection approach (29). Laparoscopic surgery performed on patients with gastric cancer, where a number of technical parameters influence long-term outcomes, has been received with scepticism. The IMIGASTRIC study was designed to investigate the oncological outcomes of minimally invasive resections in gastric cancer, based on a multicentre, prospective registry (30). Studies over the past decade have consistently reported on long-term and oncological outcomes following laparoscopic GIST resection in recognition of the clinical importance of this approach.

In the absence of randomized controlled trials, conclusions need to be drawn based on the findings of single-centre, retrospective studies. Hence, the present study aimed to conduct an objective and critical review of current evidence. Over the past 5 years, 10 studies were identified that reported a comparison between laparoscopic and open GIST resection without focusing on tumour size. The current results confirmed that the laparoscopic approach was feasible and safe. The reported conversion rate was 0 in most studies and in the three that reported a higher rate, this value never exceeded 10% (17,25). This is encouraging considering the reported average conversion rate of 10.1% for laparoscopic gastrectomy (31) and 14% for major colorectal surgery

(32). It is also important to highlight that the aforementioned studies reporting a conversion rate of >0 were those that had the smallest sample size and the lowest MINORS score. In terms of postoperative complications, the majority of studies and especially those with higher MINORS scores, reported a Dindo-Clavien III-IV complication rate of ~2% which is well below the respective rate in major colorectal and gastric surgery (31,32). Data on procedure duration, intra-operative blood loss and length of stay were almost consistently in favour of the laparoscopic approach. As most surgeons that perform these types of procedures are now well into the plateau phase of their practical training, operation duration is ~2 h on average, blood loss does not exceed 100 ml and length of hospital stay does not exceed 10 days on average, which on most occasions was 2-3 days shorter than respective open resection groups.

With regards to the more topical questions of long-term outcomes, it should be stated that only one study followed-up patients for >5 years (21). Regarding the outcomes of 5-year survival and 5-year recurrence free survival, only this single study provided reliable results (21). Unfortunately, this study reported only on 5-year recurrence free survival, which was 92.1% for the laparoscopic group and 88.9% for the open resection group, with a sample size of 126 patients. This difference was statistically insignificant. It can be argued that 5-year survival should be fairly high, given that patients have effective treatment options even after recurrence. In fact, the studies that did examine 5-year survival reported rates of 93-100% for the laparoscopic group and 86-99% for the open resection group; however, this difference was not statistically significantly different. Two of these studies had a sample size of >200 patients and MINORS scores of 12 (19,23). Only one study reported DFS and OS in detail (24). With a propensity score derived from 160 patients, this study presented a median DFS of 97 months and a median OS of ~100 months. However, the respective numbers for the open resection group were 112 and 115 months, respectively, making the DFS significantly higher than that of laparoscopic group. This is the only study that reported a significantly improved long-term outcome for the open resection group. In a study by Xiong *et al* (19) comprising 426 patients, significantly improved DFS and OS was reported for the laparoscopic group. However, these results should be considered with scepticism, as firstly no exact numbers were reported and secondly, when propensity score matching was implemented on the same cohort, this statistical significance was removed. This may mean that bias existed, and consequently results from propensity score matched analyses should be considered more reliable in this setting.

8. Conclusions and limitations

Overall, there was an even distribution of studies across the MINORS scoring system. The most common reason for missed points was reporting loss to follow-up. This is a consistent issue with

retrospective studies; however, it is also an index of good practice, from a clinical and research point of view. Particularly when examining long-term outcomes, it is important to implement an adequately long follow-up period as well as to limit or at least report the number of patients that were lost to follow-up. A minimum follow-up of 5 years and a loss to follow-up of <5% are the ideal targets. Another consistent issue with the studies assessed in the current review was design and data collection. It is inevitable that retrospective studies will suffer from various types of bias. Moreover, in the context of follow-up and subsequent treatments, there was also an inconsistency regarding the management of metastatic disease, which certainly affects overall outcomes. Specifically, although the general consensus is that patients with metastatic disease should be treated with systematic chemotherapy, it is argued that for patients with oligometastatic disease and a good response to systematic treatment, metastasectomy might be of benefit (33). Accordingly, such a stratification needs to be resolved in future studies. All the above methodological concerns can be limited by designing a prospective study with pre-agreed perioperative protocols and data collection pro formas. Propensity score matching is also a method that can compensate for certain types of bias, as explained above. Therefore, an ideal assessment would be performed as a randomized controlled study; however, the rarity of these lesions would certainly involve a multicentre design.

Several other questions were posed in the literature but were not examined in the present study, either because they were outside its scope or because there were not enough data. One key point is tumour size. Although studies have confirmed the safety of laparoscopic resections of tumours >5 cm, which was initially considered a cut-off, larger lesions are now being treated in this manner, despite there being an unknown oncological impact. Of the examined studies, two included tumours >10 cm (19,23). The results of these studies were comparable to those of studies including smaller tumours; however, a stratification based on size is lacking in the literature and would yield interesting results. Moreover, surgical technique varied among studies. In certain articles, a combined endoscopic and laparoscopic approach was implemented (20). Authors argue that this approach improved the localization of tumours and improved perioperative outcomes. However, the examined comparison was between endoscopic/laparoscopic resection versus open resection. The design that would answer the question of whether endoscopy significantly improves outcomes would involve a comparison between endoscopic/laparoscopic resection versus laparoscopic resection alone. These two important aspects should be reported in an objective and detailed manner in future studies to acquire more evidence.

Since this was a systematic review of non-randomized studies, a quantitative conclusion cannot be drawn. The heterogeneity of study design, the frequent shortcomings of reported studies

and the inconsistencies in reporting relevant outcomes, limit the clinical implementation of the present result. However, the present review confirmed the perioperative advantages of GIST laparoscopic resection, which was a consistent finding among most included studies. Moreover, the current study identified discrepancies in regard to oncological outcomes and attempted to grade the reliability of relevant studies, concluding that one study that questioned the oncological safety of laparoscopic resection may be considered more reliable than those that supported opposite findings. Finally, the current study emphasized the most important shortcomings of current literature, including follow-up and study design, and provided suggestions for the improvement of further studies to produce more credible evidence.

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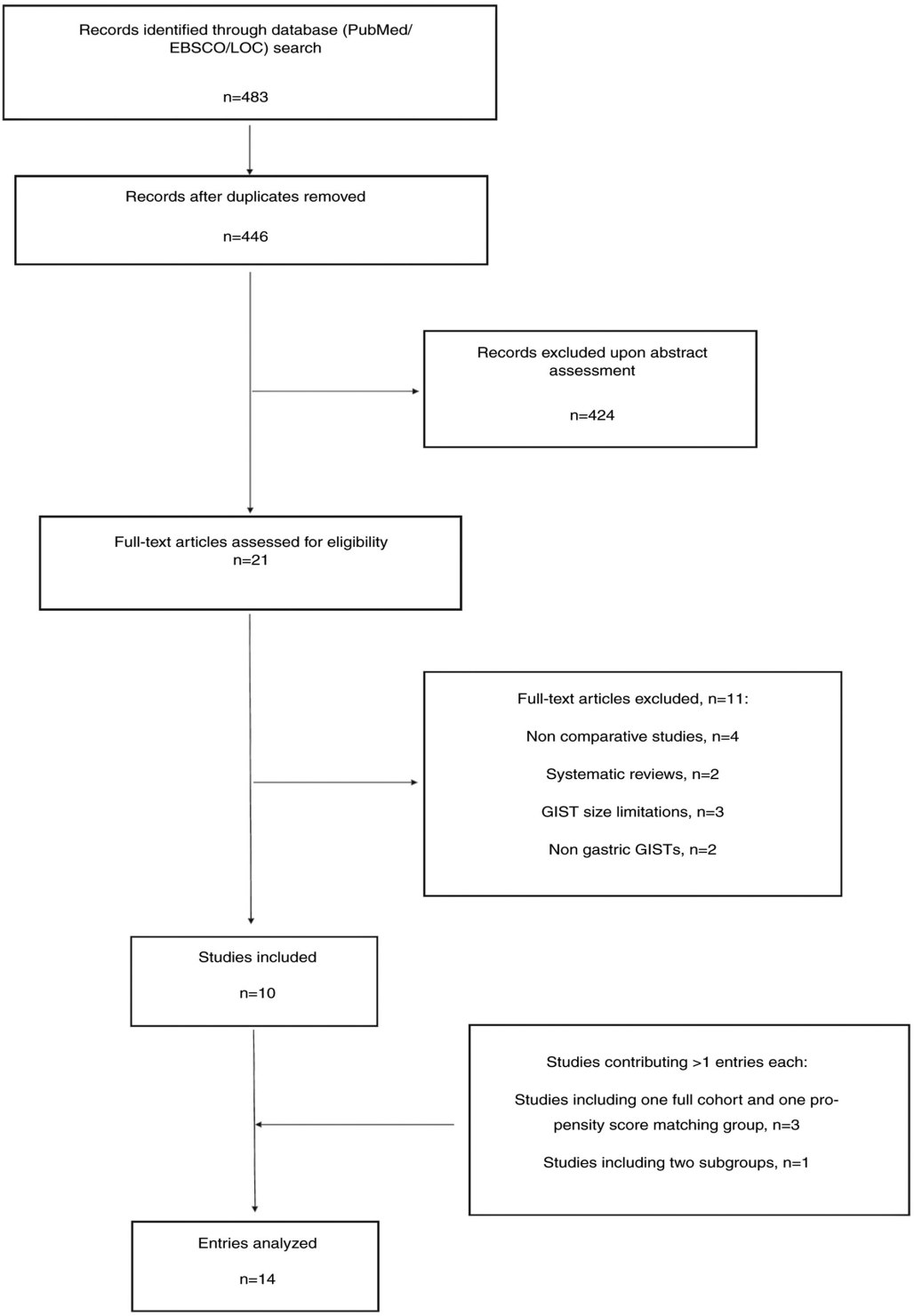
APPENDIX A

Figure legends

Figure 1. Flow chart of the article selection process, demonstrating number of articles originally yielded by literature search, number of excluded articles and respective reasons for exclusions, as well as additions due to complex dataset analysis.



APPENDIX B

Tables

Table I. Included studies, design characteristics and main epidemiological parameters.

First author, year	Span	Design	n	n, lap vs. open	Sex, male %, lap vs. open	Age, median in years, lap vs. open	Size, max cm, lap vs. open	Conversion, %	(Ref.)
Chen *et al*, 2016	2006-2012	retrospective	214	133 vs. 81	32.70 vs. 18.69	59.10 vs. 57.40	>10.00 vs. >10.00	NA	(23)
	2006-2012	after PSM	142	71 vs. 71	26.05 vs. 26.05	57.90 vs. 57.30	>10.00 vs. >10.00	NA	
Hu *et al*, 2016	2009-2014	prospective	181	93 vs. 88	55.00 vs. 48.00	61.10 vs. 63.28	5.93 vs. 6.08	0	(16)
Xu *et al*, 2016	2005-2014	retrospective	88	44 vs. 44	47.70 vs. 43.20	55.10 vs. 57.40	7.00 vs. 7.40	0	(22)
Chi *et al*, 2017	2006-2015	retrospective	126	63 vs. 63	39.70 vs. 39.70	58.50 vs. 58.02	6.35 vs. 6.07	0	(21)
Huang *et al*, 2017	2006-2014	retrospective	214	133 vs. 81	NA	NA	NA	NA	(20)
	2006-2014	favourable	140	90 vs. 50	52.22 vs. 52.00	58.80 vs. 56.60	7.40 vs. 10.30	0	
	2006-2014	unfavourable	74	43 vs. 31	53.48 vs. 45.16	59.50 vs. 58.70	6.80 vs. 8.20	0	
Ye *et al*, 2017	2005-2014	retrospective	224	102 vs. 122	42.15 vs. 43.44	NA	14.00 vs. >10.00	NA	(24)
	2005-2014	after PSM	160	80 vs. 80	45.00 vs. 41.25	NA	14.00 vs. >10.00	NA	
Wakamatsu *et al*, 2018	2003-2015	retrospective	89	65 vs. 24	54.00 vs. 62.00	66.00 vs. 69.50	5.00 vs. 12.60	3.07	(17)
Xiong *et*	2005-	retrospective	426	185 vs. 241	50.80 vs. 55.20	57.38 vs. 56.90	>10.00 vs.	0	(19)

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al, 2019	2017						>10.00		
	2005-2017	after PSM	256	128 vs. 128	53.10 vs. 50.00	58.23 vs. 57.98	>10.00 vs. >10.00	0	
Stanek *et al*, 2019	2002-2017	retrospective	68	46 vs. 22	28.30 vs. 36.40	67.00 vs. 65.00	5.50 vs. 7.00	0	(18)
Mazer *et al*, 2020	2000-2018	retrospective	77	53 vs. 24	NA	NA	4.00 vs. 7.00	8.00	(25)

PSM, propensity score matching; NA, not available.

Table II. Perioperative outcomes.

First author, year	R0, %, lap vs. open	Duration, median min, lap vs. open	Blood loss, median mls, lap vs. open	LoS, median days, lap vs. open	Complications, III-IV %, lap vs. open	(Ref.)
Chen *et al*, 2016	100 vs. 100	111.00 vs. 190.00[a]	35.00 vs. 297.00[a]	8.60 vs. 13.40[a]	2.30 vs. 2.50	(23)
	100 vs. 100	115.00 vs. 186.00[a]	36.00 vs. 290.00[a]	8.80 vs. 13.30[a]	2.80 vs. 1.40	
Hu *et al*, 2016	100 vs. 100	103.00 vs. 172.00[a]	100.00 vs. 144.00[a]	7.90 vs. 12.80[a]	8.80 vs. 16.50	(16)
Xu *et al*, 2016	NA	90.40 vs. 118.10[a]	93.50 vs. 108.10[a]	6.00vs. 9.70[a]	NA	(22)
Chi *et al*, 2017	100 vs. 100	87.46 vs. 119.58[a]	36.80 vs. 115.50[a]	6.10 vs. 8.60[a]	NA	(21)
Huang *et al*, 2017	NA	107.30 vs. 187.00[a]	35.20 vs. 263.80[a]	8.30 vs. 12.40[a]	2.20 vs. 0	(20)
	NA	119.00 vs. 197.40[a]	35.20 vs. 350.60[a]	9.50 vs. 14.90[a]	2.30 vs. 6.50	
Ye *et al*, 2017	NA	NA	NA	NA	NA	(24)
	NA	90.83 vs. 118.38[a]	91.88 vs. 121.25[a]	9.26 vs. 11.73[a]	NA	
Wakamatsu *et al*, 2018	100 vs. 100	108.00 vs. 108.00	32.50 vs. 100.00[a]	3.00 vs. 6.00[a]	9.00 vs. 12.00	(17)
Xiong *et al*, 2019	100 vs. 100	121.97 vs. 698.67[a]	NA	10.04 vs. 13.75[a]	1.62 vs. 1.65	(19)
	100 vs. 100	125.53 vs. 102.94[a]	NA	10.21 vs. 12.56[a]	2.34 vs. 0	
Stanek *et al*, 2019	100 vs. 100	100.00 vs. 95.00	25.00 vs. 175.00[a]	3.00 vs. 9.00[a]	4.30 vs. 0	(18)
Mazer *et al*, 2020	100 vs. 95.83	117.00 vs. 104.00	NA	3.00 vs. 7.00[a]	1.88 vs. 8.33	(25)

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[a]P<0.05; LoS, length of hospital stay; NA, not applicable. Rate of complications reported regarding Dindo-Clavien III-IV cases.

Table III. Follow-up and long-term outcomes.

First author, year	F-up, median months, lap vs. open	Recurrence, %, lap vs. open	DFS, median months, lap vs. open	5-year recurrence-free survival rate, %, lap vs. open	Mortality, %, lap vs. open	OS, median months, lap vs. open	5-year survival rate, %, lap vs. open	(Ref.)
Chen *et al*, 2016	35.00 vs. 35.00	6.80 vs. 13.60	NA	82.20 vs. 86.10	NA	NA	95.40 vs. 85.90	(23)
	36.00 vs. 36.00	8.50 vs. 7.00	NA	82.50 vs. 91.90	NA	NA	93.10 vs. 91.90	
Hu *et al*, 2016	32.00 vs. 34.20	13.18 vs. 21.17	NA	NA	4.00 vs. 7.00	NA	NA	(16)
Xu *et al*, 2016	NA	0 vs. 4.50	98.30 vs. 98.10	NA	2.30 vs. 4.50	NA	100 vs. 95.00	(22)
Chi *et al*, 2017	64.00 vs. 67.00	9.52 vs. 15.87	NA	92.10 vs. 88.90	6.35 vs. 7.94	NA	NA	(21)
Huang *et al*, 2017	40.00 vs. 40.00	NA	NA	NA	NA	NA	NA	(20)
	40.00 vs. 40.00	NA	NA	NA	NA	NA	NA	
Ye *et al*, 2017	NA	NA	NA	NA	NA	NA	NA	(24)
	35.3 vs. 40.99	3.75 vs. 5.00	97.04 vs. 111.61[a]	97.50 vs. 96.25	1.25 vs. 2.50	99.65 vs. 115.26[a]	98.75 vs. 98.75	
Wakamatsu, *et al*, 2018	32.60 vs. 24.70	0 vs. 8.33	NA	NA	3.07 vs. 8.33	non-significant	NA	(17)
Xiong *et al*, 2019	43.00 vs. 43.00	NA	lap > open[a]	NA	NA	lap > open[a]	NA	(19)
	43.00 vs.	NA	non-significant	93.90 vs. 81.70	NA	non-significant	95.90 vs. 89.70	

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	43.00							
Stanek *et al*, 2019	57.00 vs. 57.00	0 vs. 22.72	NA	NA	13.63 vs. 2.17	NA	NA	(18)
Mazer *et al*, 2020	NA	NA	NA	NA	NA	NA	NA	(25)

[a]P<0.05; F-up, follow-up; DFS, disease-free survival; OS, overall survival; NA, not available.

Table IV. Evaluation of included studies according to MINORS criteria.

First author, year	Study aim	Consecutive patients	Data collection methodology	Reported endpoints	Outcome evaluation bias	Equivalent groups	Statistical methods	Follow-up period	Patients lost to follow-up	Total
Chen *et al*, 2016	1	0	1	2	2	2	2	2	0	12
Hu *et al*, 2016	2	1	2	1	0	0	2	1	0	9
Xu *et al*, 2016	2	2	1	2	2	2	2	2	0	15
Chi *et al*, 2017	2	2	1	2	1	2	2	2	0	14
Huang *et al*, 2017	2	0	1	2	1	0	2	2	1	11
Ye *et al*, 2017	2	2	1	2	2	2	2	2	0	15
Wakamatsu	2	0	1	2	0	0	2	1	0	8

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et al, 2018										
Xiong *et al*, 2019	2	0	0	2	2	2	2	2	0	12
Stanek *et al*, 2019	2	0	1	2	0	0	2	1	0	8
Mazer *et al*, 2020	0	0	1	2	0	0	2	0	0	5