Safety of fast-track rehabilitation after gastrointestinal surgery: Systematic review and meta-analysis

Liu-Hua Wang, Fang Fang, Chun-Ming Lu, Dao-Rong Wang, Ping Li, Ping Fu

Liu-Hua Wang, Department of General Surgery, Yizheng People’s Hospital, Yangzhou 211400, Jiangsu Province, China
Fang Fang, Dao-Rong Wang, Ping Fu, Department of Gastrointestinal Surgery, Subei People’s Hospital of Jiangsu Province, the First Affiliated Hospital of Yang Zhou University, Yangzhou 225001, Jiangsu Province, China
Chun-Ming Lu, Ping Li, Department of General Surgery, Armed Police Corps Hospital of Jiangsu, Yangzhou 225003, Jiangsu Province, China

Author contributions: Wang LH, Fang F and Lu CM contributed equally to this study; Wang LH, Fang F and Lu CM conceived and designed the review, conducted the statistical analyses and contacted authors of included studies to obtain additional information, and drafted the manuscript; Fu P provided supervision; Wang LH, Fang F, Lu CM, Wang DR and Li P identified and acquired reports of trials, analyzed data and assessed risk of bias; all of the authors contributed to the interpretation of data, critically revised the manuscript, and approved the final version of the manuscript submitted for publication and are guarantors for the study.

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Correspondence to: Ping Fu, BM, Department of Gastrointestinal Surgery, Subei People’s Hospital of Jiangsu Province, the First Affiliated Hospital of Yang Zhou University, 98 Nantong West Road, Yangzhou 225001, Jiangsu Province, China.
Telephone: +86-514-87373282 Fax: +86-514-87373282
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Abstract

AIM: To compare the safety of fast-track rehabilitation protocols (FT) and conventional care strategies (CC), or FT and laparoscopic surgery (LFT) and FT and open surgery (OFT) after gastrointestinal surgery.

METHODS: We searched MEDLINE, WHO International Trial Register, Embase and The Cochrane Central Register of Controlled Trials up to 2014 for randomized controlled trials (RCTs) comparing FT and CC or comparing LFT and OFT, with 10 or more randomized participants and about 30 d follow-up. Two reviewers independently extracted data on complications, anastomotic leak, obstruction, wound infection, re-admission between FT and CC or LFT and OFT after gastrointestinal surgery.

RESULTS: Twenty-four RCTs of FT vs CC or LFT vs OFT were included. Compared with CC, FT reduced overall complications and wound infection. However, anastomotic leak, obstruction and re-admission were not significantly reduced. The pooled risk ratio (RR) of 0.69 (95%CI: 0.60-0.78; P < 0.001), pooled RR of 0.71 (95%CI: 0.57-0.88; P < 0.001), pooled RR of 0.93 (95%CI: 0.68-1.25; P > 0.05), a pooled RR of 0.87 (95%CI: 0.67-1.15; P > 0.05) and pooled RR of 0.94 (95%CI: 0.73-1.22; P > 0.05) respectively. Compared with OFT, LFT reduced complications, with a pooled RR of 0.66 (95%CI: 0.54-0.81; P < 0.001).

CONCLUSION: FTs are safe after gastrointestinal surgery. Additional large, prospective RCTs should be conducted to establish further the safety of this approach.

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Key words: Fast-track rehabilitation protocols; Laparoscopic surgery; Open surgery; Enhanced recovery; Gastrointestinal surgery; Complications; Readmission; Anastomotic leak; Wound infection; Obstruction

Core tip: Fast-track rehabilitation protocols (FT) after gastrointestinal surgery have become the most fashionable method of treatment for gastrointestinal malignancy. Complications after FT for gastrointestinal resection have been discussed in China as well as other countries. This study clarified that compared with conventional care strategies, FT has a low level of complications and similar incidence of re-admission of about 1 mo.

Wang LH, Fang F, Lu CM, Wang DR, Li P, Fu P. Safety of fast-track rehabilitation after gastrointestinal surgery: Systematic review and meta-analysis. World J Gastroenterol 2014;
The search was limited to randomized controlled trials and surgery. The last search was done on March 1, 2014.

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achieve early recovery after gastrointestinal surgery, with no more than two CCs. When a study reporting the same patient cohort was included in several publications, only the most recent or complete study was selected.

The exclusion criteria were: (1) case reports; (2) articles that were not full text or were non-comparative studies; (3) more than two CCs were included; and (4) the FT included no more than seven of the 20 FT items.

Study selection

RCTs met the inclusion criteria if they involved the FT for gastrointestinal malignant disease in adult patients and used CCs for control. Both full-length publications and abstracts were selected. Letters, reviews without original data and animal studies were excluded. If any doubt about suitability remained after the abstract was examined, the full manuscript was obtained.

Data extraction

All included studies were assessed for the quality of their methodology and relevance to the objective of our meta-analysis. Conduct and reporting were in accordance with the QUOROM statement. Data on complications (anastomotic leak, wound infection, obstruction) and re-admission from each trial were extracted and compared independently by the two investigators.

Assessment of risk of bias

To identify potential sources of bias in the reported events, we followed the Cochrane Collaboration’s risk of bias framework[14] and considered for each trial the following risk domains: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and study investigators for the outcomes of interest); (3) detection bias (blinding of outcome assessors); (4) attrition bias (incomplete out-

INTRODUCTION

In recent years, fast-track rehabilitation protocols (FT) have frequently appeared in the literature. The concept of FT was first proposed by a Danish surgeon, Kehlet, with the intent to reduce stress, complications, and hospital stay after gastrointestinal surgery.[1,2]

FT was investigated initially in the setting of elective gastrointestinal surgery, where it was shown that, by optimizing and standardizing perioperative care, median length of hospital stay could be reduced from 8-12 d to 2-4 d.[3-5]. For the surgical treatment of gastrointestinal malignant disease, conventional elective gastrointestinal resection is associated with a complication rate of 10%–45% and a postoperative hospital stay of 8-13 d.[6-10]. It has been established that a higher rate of serious postoperative complications is associated with an excessive response to surgical stress[11,12] and that C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-α and resting energy expenditure (REE) may act as markers for the severity of the surgical stress response.[14,15]. To improve this problem, FT has been developed.[16-20]. FT is based on the reduction of surgical stress by various surgical and anesthetic approaches to enhance recovery.

In a prospective study investigating the value of an accelerated recovery program in elective gastrointestinal resection, Grantcharov and Kehlet[23] demonstrated that a number of the principles of FT, such as avoidance of prophylactic nasogastric tubes and abdominal drains, early postoperative feeding, and use of multimodal analgesia, could be applied successfully in this clinical setting without increasing postoperative morbidity[23]. The safety of FT has been fiercely disputed. Therefore, the primary aim of this meta-analysis was to evaluate the safety of FT vs conventional care strategies (CC) or FT and laparoscopic surgery (LFT) vs FT and open surgery (OFT), as measured by the rate of complications, specifically anastomotic leaks, wound infection, obstruction and re-admission. The secondary aim was to understand the difficulties, limitations, or advantages of FT for gastrointestinal surgery.

MATERIALS AND METHODS

Publication search

Relevant studies were identified by searching the following data: MEDLINE (1985 until present), WHO International Trial Register (1985 until present), Embase (1985 until present) and The Cochrane Central Register of Controlled Trials (1985 until present). The medical subject headings (MeSH) and keywords searched for individually in combination were as follows: “fast track” or “enhanced recovery” and “colorectal and surgery” or “gastric and surgery”. The last search was done on March 1, 2014. The search was limited to randomized controlled trials (RCTs) with about 30-d follow-up, but without age, sex and weight. Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Internet search engines were also used to perform a manual search for abstracts from international meetings, which were then downloaded and studied.

Inclusion and exclusion criteria

The inclusion criteria for the study were: (1) RCTs; (2) detailed patient information provided; and (3) to be considered FT; a rehabilitation protocol had to include at least seven of the 20 FT items in the FT group (preoperative counseling, preoperative feeding, no premedication, no bowel preparation, fluid restriction, symbiotics administered before surgery, no preoperative fasting but provision of clear carbohydrate-enriched liquids until 2 h before surgery, multi-way anesthetic techniques, high inspired oxygen concentrations, avoidance of perioperative fluid overload, short/transverse incisions, maintenance of body temperature, no routine use of drains, non-opioid analgesia and nasogastric decompression tubes, standard laxatives, early removal of bladder catheters and prokinetics, and early postoperative mobilization and feeding[26] ) to achieve early recovery after gastrointestinal surgery, with no more than two CCs.

When a study reporting the same patient cohort was included in several publications, only the most recent or complete study was selected.

The exclusion criteria were: (1) case reports; (2) articles that were not full text or were non-comparative studies; (3) more than two CCs were included; and (4) the FT included no more than seven of the 20 FT items.

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To identify potential sources of bias in the reported events, we followed the Cochrane Collaboration’s risk of bias framework[24] and considered for each trial the following risk domains: (1) selection bias (random sequence generation and allocation concealment); (2) performance bias (blinding of participants and study investigators for the outcomes of interest); (3) detection bias (blinding of outcome assessors); (4) attrition bias (incomplete out-
come data); and (5) reporting bias (selective outcome reporting). Risk of bias for each domain was categorized as low, unclear, or high. This information was used to make judgments about the overall risk of bias for each trial. We followed the Cochrane Collaboration’s recommendation to make judgments on the basis of whether the ranking of the level of bias across domains could have led to any material bias on the outcomes of interests and, where applicable, what the direction of the bias would likely be.

Statistical analysis
Statistical analysis was conducted using Review Manager version 5.0.0 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were used to assess complications (anastomotic leaks, wound infection, and obstruction) and re-admission. Statistical heterogeneity was assessed with a χ² test, for which P < 0.1 was considered statistically significant. The I² statistic was used to assess the impact of heterogeneity on the meta-analysis. If the test of heterogeneity was statistically significant, then the random-effects model was used; otherwise, a fixed-effects model was used. Two-sided P values < 0.05 were considered statistically significant. Funnel plots and Egger’s test were used to evaluate publication bias.

RESULTS
Search results
Five hundred and ninety-six references were identified from the medical journal databases. On examination of the abstracts, 485 articles were rejected based on the criteria outlined in Figure 1. Assessment of the complete text of the 87 remaining articles led to the elimination of 25 papers that contained no data pertaining to the outcome of LFT for colorectal resection, and 24 that were not RCTs. Nine had fewer than seven items of FT, 12 papers were of animal studies, and 17 papers explained the effect of analgesia. The remaining 24 nonduplicated RCTs that compared FT with CC were included in the meta-analysis.

Characteristics of the selected RCTs
Characteristics of the 24 RCTs included in the meta-analysis are summarized in Table 1. The bias of included studies was low (Table 2). These studies were published between 1985 and 2013 and investigated a total of 3365 patients, 2093 of whom received an FT and 1272 of whom received a CC. Nineteen of the studies compared FT and CC for colorectal resection (2538 patients), 15 of the studies compared OFT and OCC for colorectal resection (1690 patients), eight of the studies compared LFT and LCC for colorectal resection (774 patients), and nine of the studies compared LFT and OFT for colorectal resection (827 patients). Two studies published by the same team from the same institute within the same study interval were regarded as one trial, but both studies were included and shared the same study number because some separately published data were complementary.

Meta-analysis results
Complications: Compared with CC, FT reduced complications. The pooled RR was 0.69 (95%CI: 0.60-0.78; P < 0.001), χ² = 95.37 (P < 0.001) and I² = 57% (Figure 2A, Table 3).

Nineteen studies (2538 patients) provided data on complications for FT vs CC; 26.7% (338/1266 patients) had complications in the FT group and 36.4% (463/1272)
We further mitigated the possible effect of any attrition bias and reporting bias at individual trial level by collection of additional unpublished prior knowledge of the investigators of the tested hypothesis in this study at the time of event collection. All analyses in this report are based on intention-reporting. Selection bias is a feature of the trial design. Performance and detection bias are overall low given that most data were collected without any arm, which could lead to missing outcome data for that trial arm over the other trial arm; and reporting bias includes the possibility of selective outcome reporting. Selection bias is based on random sequence generation and allocation concealment; performance bias includes blinding of participants and study outcomes; detection bias is based on blinding of participants and study outcomes; reporting bias includes selective outcome reporting.

### Table 1  Main characteristics of the 24 included studies

| Ref.         | Way   | Year | No.  | Age (yr) | Sex (M:F) |
|--------------|-------|------|------|----------|-----------|
|              | CC    | FT   | CC   |          |           |
| Ionescu et al[35] | Open  | 2009 | 48   | 60.94 ± 9.9 | 63.1 ± 12.19 | 30:18 | 31:17 |
| Ren et al[44]   | Open  | 2012 | 299  | 59      | 61       | 178:121 | 190:108 |
| Yang et al[47]  | Open  | 2012 | 32   | 57.2 ± 11.70 | 59.5 ± 12.10 | 20:12 | 22:8 |
| Hübner et al[48] | Open  | 2010 | 36   | 60      | 61       | 18:18 | 17:14 |
| Wang et al[49]  | Open  | 2012 | 41   | 57.2 ± 18.1 | 55.4 ± 16.8 | 24:17 | 25:17 |
| Vlug et al[50]  | Open  | 2011 | 93   | 66 ± 10.3 | 66 ± 7.1 | 54:39 | 59:39 |
| van Bree et al[51] | Lap  | 2011 | 18   | 64 ± 10.1 | 66 ± 6.9 | 11:7 | 11:7 |
| Veenhof et al[52] | Lap  | 2012 | 17  | 65      | 68       | 9:8 | 14:6 |
| Serclová et al[53] | Lap/open | 2009 | 51   | 35.1 ± 11.0 | 37.6 ± 12.5 | 20:31 | 32:20 |
| Muller et al[46] | Lap/open | 2009 | 76   | 62      | 59       | 37:39 | 40:35 |
| Wang et al[54]  | Lap/open | 2011 | 40   | 71      | 72       | 22:18 | 20:18 |
| Wang et al[55]  | Lap/open | 2011 | 106  | 57      | 55       | 65:41 | 60:44 |
| King et al[56]  | Lap/open | 2008 | 41   | 72.3    | 70.4    | 23:18 | 8:11 |
| Faiz et al[57]  | Lap/open | 2008 | 191  | 67.9 ± 14.1 | 66.3 ± 13.7 | 20:30 | 98:95 |
| Srinivasa et al[58] | Lap/open | 2013 | 37   | 69 ± 16 | 72 ± 12 | 19:18 | 22:15 |
| Basse et al[44] | Lap/open | 2005 | 30   | 75.5    | 75       | 14:16 | 14:16 |
| MacKay et al[59] | Lap/open | 2006 | 22   | 72      | 73.2    | 12:10 | 25:33 |
| García-Botello et al[60] | Lap/open | 2011 | 61   | 62      | 60       | 40:21 | 32:26 |
| Anderson et al[61] | Open  | 2005 | 14   | 64      | 68       | 6:86 | 5:6 |
| Gatt et al[62]  | Open  | 2005 | 19   | 67      | 67       | 14:6 | 9:10 |
| Khoo et al[36]  | Open  | 2007 | 35   | 69.3    | 73       | 12:23 | 15:20 |
| Wang et al[63]  | Open  | 2010 | 47   | 58.76 ± 9.66 | 56.87 ± 9.16 | 32:133 | 29:18 |
| Chen Hu et al[64] | Lap/open | 2012 | 40   | 59/64   | 62.5/64.5 | 19:21 | 22:20 |
| Lemanu et al[65] | Lap  | 2012 | 38   | 43.5    | 43.9     | 13:27 | 10:28 |

Lap: Laparoscopy.

### Table 2  Risk-of-bias assessment of the randomized controlled trials

| Ref.         | Selection bias | Performance bias | Detection bias | Attrition bias | Reporting | Overall risk of bias |
|--------------|----------------|------------------|----------------|---------------|----------|---------------------|
| Ionescu et al[35] | Low            | Low              | Low            | Low           | Low      | Low                 |
| Ren et al[44]   | Low            | Unclear          | Low            | Low           | Low      | Low                 |
| Yang et al[47]  | Low            | Low              | Low            | Unclear       | Low      | Low                 |
| Hübner et al[48] | Low            | Low              | Low            | Low           | Low      | Low                 |
| Wang et al[49]  | Low            | Low              | Low            | Low           | Unclear  | Low                 |
| Vlug et al[50]  | Unclear        | Low              | Low            | Low           | Low      | Low                 |
| van Bree et al[51] | Low            | Low              | Low            | Low           | Unclear  | Low                 |
| Veenhof et al[52] | Low            | Low              | Unclear        | Low           | Low      | Low                 |
| Serclová et al[53] | Low            | Low              | Low            | Unclear       | Low      | Low                 |
| Muller et al[46] | Low            | Low              | Low            | Low           | Low      | Low                 |
| Wang et al[54]  | Low            | Low              | Low            | Low           | Low      | Low                 |
| Wang et al[55]  | Unclear        | Low              | Low            | Low           | Low      | Low                 |
| King et al[56]  | Low            | Un unclear       | Low            | Low           | Low      | Low                 |
| Faiz et al[57]  | Low            | Low              | Low            | Unclear       | Low      | Low                 |
| Srinivasa et al[58] | Low            | Unclear          | Low            | Low           | Low      | Low                 |
| Basse et al[44] | Unclear        | Low              | Low            | Low           | Low      | Low                 |
| MacKay et al[59] | Low            | Low              | Low            | Low           | Low      | Low                 |
| García-Botello et al[60] | Low            | Low              | Low            | Low           | Unclear  | Low                 |
| Anderson et al[61] | Low            | Low              | Low            | Low           | Low      | Low                 |
| Gatt et al[62]  | Low            | Unclear          | Low            | Low           | Low      | Low                 |
| Khoo et al[36]  | Low            | Low              | Low            | Low           | Low      | Low                 |
| Wang et al[63]  | Low            | Low              | Low            | Low           | Low      | Low                 |
| Chen Hu et al[64] | Low            | Low              | Low            | Low           | Low      | Low                 |
| Lemanu et al[65] | Low            | Low              | Low            | Unclear       | Low      | Low                 |

Selection bias is based on random sequence generation and allocation concealment; performance bias includes blinding of participants and study investigators for the outcomes of interest; detection bias includes blinding of outcome assessors; attrition bias indicates systematic loss of participants in one arm, which could lead to missing outcome data for that trial arm over the other trial arm; and reporting bias includes the possibility of selective outcome reporting. Selection bias is a feature of the trial design. Performance and detection bias are overall low given that most data were collected without any prior knowledge of the investigators of the tested hypothesis in this study at the time of event collection. All analyses in this report are based on intention-to-treat and we further mitigated the possible effect of any attrition bias and reporting bias at individual trial level by collection of additional unpublished data.
in the CC group. Pooling the results indicated that FT significantly reduced complications compared with CC. The weighted mean difference (WMD) was 0.67 (95%CI: 0.56-0.82, \( P < 0.001 \)), \( \chi^2 = 42.76 \) (\( P = 0.0009 \)) and \( I^2 = 58\% \), indicating heterogeneity among the studies.

Fifteen studies (1690 patients) provided data on complications for OFT vs OCC; 25% (211/847 patients) had complications in the OFT group and 32.6% (275/843) in the OCC group. Pooling the results indicated that OFT significantly reduce complications compared with OCC. The WMD was 0.97 (95%CI: 0.60-1.73, \( P < 0.001 \)), \( \chi^2 = 3.68 \) (\( P = 0.05 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Eight studies (774 patients) provided data on complications for LFT vs LCC; 26.5% (101/382 patients) had complications in the LFT group and 34% (133/392) in the LCC group. Pooling the results indicated that LFT significantly reduce complications compared with LCC. The WMD was 0.67 (95%CI: 0.32-1.42, \( P < 0.05 \)), \( \chi^2 = 18.33 \) (\( P = 0.01 \)) and \( I^2 = 62\% \), indicating heterogeneity among the studies.

Eight studies (586 patients) provided data on complications for LFT vs OFT; 23.9% (69/289 patients) had complications in the LFT group and 33% (98/297) in the OFT group. Pooling the results indicated that LFT significantly reduce complications compared with OFT. The WMD was 0.72 (95%CI: 0.56-0.92, \( P < 0.05 \)), \( \chi^2 = 9.16 \) (\( P = 0.01 \)) and \( I^2 = 24\% \), which excludes heterogeneity among the studies.

Anastomotic leak: Compared with CC, FT reduced anastomotic leaks. The pooled RR was 0.93 (95%CI: 0.68-1.25; \( P > 0.05 \)), \( \chi^2 = 9.95 \) (\( P = 0.99 \)) and \( I^2 = 0\% \) (Figure 2B, Table 3).

Eleven studies (1393 patients) provided data on anastomotic leaks for FT vs CC; 3.7% (36/966 patients) had anastomotic leaks in the FT group and 4.1% (40/973) in the CC group. Pooling the results indicated that FT did not significantly reduce anastomotic leaks compared with CC. The WMD was 0.92 (95%CI: 0.60-1.43, \( P > 0.05 \)), \( \chi^2 = 3.68 \) (\( P = 0.06 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Nine studies (1364 patients) provided data on anastomotic leaks for OFT vs OCC; 3.4% (23/683 patients) had complications in the OFT group and 3.8% (26/681) in the OCC group. Pooling the results indicated that OFT did not significantly reduce anastomotic leaks compared with OCC. The WMD was 0.90 (95%CI: 0.53-1.53, \( P > 0.05 \)), \( \chi^2 = 3.44 \) (\( P = 0.09 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Five studies (575 patients) provided data on anastomotic leaks for LFT vs LCC; 4.6% (13/283 patients) had anastomotic leaks in the LFT group and 4.8% (14/292) in the LCC group. Pooling the results indicated that LFT did not significantly reduce anastomotic leaks compared with LCC. The WMD was 0.98 (95%CI: 0.48-2.01, \( P > 0.05 \)), \( \chi^2 = 2.73 \) (\( P = 0.60 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Six studies (626 patients) provided data on anastomotic leaks for LFT vs OFT; 3.8% (15/399 patients) had anastomotic leaks in the LFT group and 5.3% (12/227) in the OFT group. Pooling the results indicated that LFT significantly reduce anastomotic leaks compared with OFT. The WMD was 0.83 (95%CI: 0.40-1.73, \( P > 0.05 \)),

### Table 3 Risk ratio and 95%CI of complications for FT vs CC during colorectal surgery in all of the patients

| Outcome or subgroup | Studies (n) | Participants (n) | Effect estimate RR (95%CI) | heterogeneity | \( I^2 \) | \( P \) value |
|---------------------|------------|-----------------|---------------------------|---------------|------|--------------|
| 1.1 Complication    |            |                 |                           |               |      |              |
| 1.1.1 FT vs CC      | 19         | 2538            | 0.67 (0.56, 0.82)         | 58\%          | 0.0009 |
| 1.1.2 OFT vs OCC    | 15         | 1690            | 0.73 (0.58, 0.93)         | 57\%          | 0.003 |
| 1.1.3 LFT vs LCC    | 8          | 774             | 0.58 (0.38, 0.88)         | 62\%          | 0.01  |
| 1.1.4 LFT vs OFT    | 8          | 586             | 0.72 (0.56, 0.92)         | 24\%          | 0.24  |
| 1.2 Anastomotic leak|            |                 |                           |               |      |              |
| 1.2.1 FT vs CC      | 11         | 1939            | 0.92 (0.60, 1.43)         | 0\%           | 0.96  |
| 1.2.2 OFT vs OCC    | 9          | 1364            | 0.90 (0.53, 1.53)         | 0\%           | 0.90  |
| 1.2.3 LFT vs LCC    | 5          | 575             | 0.98 (0.48, 2.01)         | 0\%           | 0.60  |
| 1.2.4 LFT vs OFT    | 6          | 626             | 0.83 (0.40, 1.73)         | 0\%           | 0.78  |
| 1.3 obstruction     |            |                 |                           |               |      |              |
| 1.3.1 FT vs CC      | 9          | 1698            | 0.87 (0.59, 1.29)         | 0\%           | 0.96  |
| 1.3.2 OFT vs OCC    | 7          | 1160            | 0.97 (0.62, 1.52)         | 0\%           | 1.00  |
| 1.3.3 LFT vs LCC    | 4          | 539             | 0.67 (0.32, 1.42)         | 0\%           | 0.62  |
| 1.3.4 LFT vs OFT    | 3          | 295             | 1.23 (0.51, 3.00)         | 0\%           | 0.40  |
| 1.4 Wound infection |            |                 |                           |               |      |              |
| 1.4.1 FT vs CC      | 14         | 2133            | 0.72 (0.52, 0.97)         | 10\%          | 0.34  |
| 1.4.2 OFT vs OCC    | 12         | 1461            | 0.72 (0.51, 1.02)         | 28\%          | 0.18  |
| 1.4.3 LFT vs LCC    | 5          | 539             | 0.64 (0.32, 1.26)         | 0\%           | 0.91  |
| 1.4.4 LFT vs OFT    | 4          | 329             | 0.51 (0.26, 1.01)         | 35\%          | 0.20  |
| 1.5 re-admission    |            |                 |                           |               |      |              |
| 1.5.1 FT vs CC      | 11         | 1468            | 0.99 (0.71, 1.43)         | 0\%           | 0.80  |
| 1.5.2 OFT vs OCC    | 8          | 781             | 1.07 (0.60, 1.91)         | 0\%           | 0.85  |
| 1.5.3 LFT vs LCC    | 5          | 613             | 0.74 (0.43, 1.28)         | 0\%           | 0.82  |
| 1.5.4 LFT vs OFT    | 6          | 671             | 0.45 (0.20, 0.71)         | 14\%          | 0.32  |
| Study or subgroup | CC     | FT     | Risk ratio M-H, random, 95%CI | Risk ratio M-H, random, 95%CI |
|------------------|--------|--------|-------------------------------|-------------------------------|
| **1.1.1 FT vs CC** |        |        |                               |                               |
| Anderson 2003    | 11     | 14     | 1.6%                          | 0.65 (0.27, 1.59)             |
| Gatt 2005        | 20     | 15     | 2.9%                          | 0.63 (0.37, 1.08)             |
| Chen Hu 2012     | 42     | 26     | 3.2%                          | 0.57 (0.35, 0.92)             |
| Hübner 2010      | 31     | 14     | 2.1%                          | 0.49 (0.24, 1.01)             |
| Lonescu 2009     | 48     | 11     | 1.5%                          | 0.55 (0.22, 1.36)             |
| Khoo 2007        | 16     | 19     | 1.8%                          | 0.56 (0.29, 1.09)             |
| Lemanu 2012      | 88     | 38     | 2.3%                          | 1.19 (0.52, 2.69)             |
| Muller 2009      | 75     | 37     | 3.2%                          | 0.43 (0.26, 0.70)             |
| Ren 2012         | 29     | 28     | 3.2%                          | 1.03 (0.63, 1.69)             |
| Serinova 2009    | 35     | 25     | 2.6%                          | 0.45 (0.25, 0.81)             |
| Srinivasa 2013   | 27     | 27     | 4.5%                          | 0.96 (0.72, 1.36)             |
| van Bree 2012    | 39     | 36     | 2.9%                          | 0.68 (0.40, 1.17)             |
| Veenhof 2012     | 14     | 17     | 2.4%                          | 0.70 (0.37, 1.34)             |
| Vlug 2011        | 193    | 132    | 5.3%                          | 1.02 (0.88, 1.18)             |
| Wang 2010        | 45     | 7      | 1.6%                          | 1.23 (0.50, 3.03)             |
| Wang 2011        | 104    | 39     | 3.3%                          | 0.50 (0.32, 0.80)             |
| Wang 2012        | 82     | 16     | 2.1%                          | 0.63 (0.31, 1.31)             |
| Wang 2013        | 38     | 8      | 0.7%                          | 0.24 (0.05, 1.05)             |
| Yang 2012        | 30     | 12     | 1.7%                          | 0.47 (0.20, 1.09)             |
| **Subtotal (95%CI)** | 1272   | 893    |                               | 0.67 (0.56, 0.82)             |

Total events: 338 463
Heterogeneity: Tau^2 = 0.08, I^2 = 42.76, df = 18 (P = 0.0009); I^2 = 58%
Test for overall effect: Z^2 = 4.05 (P < 0.0001)

| **1.1.2 OFT vs OCC** |        |        |                               |                               |
| Anderson 2003    | 11     | 14     | 1.6%                          | 0.65 (0.27, 1.59)             |
| Gatt 2005        | 20     | 15     | 2.9%                          | 0.63 (0.37, 1.08)             |
| Chen Hu 2012     | 42     | 26     | 3.2%                          | 0.57 (0.35, 0.92)             |
| Hübner 2010      | 31     | 14     | 2.1%                          | 0.49 (0.24, 1.01)             |
| Lonescu 2009     | 48     | 11     | 1.5%                          | 0.55 (0.22, 1.36)             |
| Khoo 2007        | 16     | 19     | 1.8%                          | 0.56 (0.29, 1.09)             |
| Lemanu 2012      | 88     | 38     | 2.3%                          | 1.19 (0.52, 2.69)             |
| Muller 2009      | 75     | 37     | 3.2%                          | 0.43 (0.26, 0.70)             |
| Ren 2012         | 29     | 28     | 3.2%                          | 1.03 (0.63, 1.69)             |
| Serinova 2009    | 35     | 25     | 2.6%                          | 0.45 (0.25, 0.81)             |
| Srinivasa 2013   | 27     | 27     | 4.5%                          | 0.96 (0.72, 1.36)             |
| van Bree 2012    | 39     | 36     | 2.9%                          | 0.68 (0.40, 1.17)             |
| Veenhof 2012     | 14     | 17     | 2.4%                          | 0.70 (0.37, 1.34)             |
| Vlug 2011        | 132    | 107    | 5.3%                          | 1.02 (0.88, 1.18)             |
| Wang 2010        | 45     | 7      | 1.6%                          | 1.23 (0.50, 3.03)             |
| Wang 2011        | 104    | 39     | 3.3%                          | 0.50 (0.32, 0.80)             |
| Wang 2012        | 82     | 16     | 2.1%                          | 0.63 (0.31, 1.31)             |
| Wang 2013        | 38     | 8      | 0.7%                          | 0.24 (0.05, 1.05)             |
| Yang 2012        | 30     | 12     | 1.7%                          | 0.47 (0.20, 1.09)             |
| **Subtotal (95%CI)** | 843    | 585    |                               | 0.73 (0.58, 0.93)             |

Total events: 211 275
Heterogeneity: Tau^2 = 0.11, I^2 = 32.76, df = 14 (P = 0.003); I^2 = 57%
Test for overall effect: Z^2 = 2.56 (P = 0.01)

| **1.1.3 LFT vs LCC** |        |        |                               |                               |
| Chen Hu 2012       | 22     | 14     | 2.3%                          | 0.58 (0.30, 1.13)             |
| Lemanu 2012        | 18     | 11     | 1.8%                          | 1.19 (0.52, 2.69)             |
| van Bree 2011      | 18     | 11     | 1.8%                          | 0.58 (0.30, 0.82)             |
| Veenhof 2012       | 23     | 9      | 0.8%                          | 0.27 (0.07, 1.10)             |
| Vlug 2011          | 109    | 60     | 4.7%                          | 0.98 (0.77, 1.26)             |
| Wang 2011          | 104    | 39     | 3.3%                          | 0.50 (0.32, 0.80)             |
| Wang 2012          | 42     | 12     | 1.8%                          | 0.69 (0.26, 1.37)             |
| Wang 2013          | 38     | 8      | 0.7%                          | 0.24 (0.05, 1.05)             |
| **Subtotal (95%CI)** | 392    | 155    |                               | 0.58 (0.38, 0.88)             |

Total events: 101 155
Heterogeneity: Tau^2 = 0.18, I^2 = 18.33, df = 7 (P = 0.01); I^2 = 62%
Test for overall effect: Z^2 = 2.53 (P = 0.01)

| **Total (95%CI)** |        |        |                               |                               |
| 2495             | 2507   | 100.0% |                               | 0.69 (0.60, 0.78)             |

Total events: 650 893
Heterogeneity: Tau^2 = 0.08, I^2 = 95.37, df = 41 (P < 0.00001); I^2 = 57%
Test for overall effect: Z^2 = 5.57 (P < 0.00001)
| Study or subgroup | Events | Total Events | Weight | Risk ratio | Risk ratio |
|------------------|--------|--------------|--------|------------|------------|
|                  | FT     | CC           |        | M-H, fixed | 95%CI      |
| 1.2.1 FT vs CC   |        |              |        |            |            |
| García-Botello 2011 | 4  | 61          | 6  | 58         | 7.5%       |
| Hübner 2010      | 0  | 36          | 1  | 31         | 2.0%       |
| Lonescu 2009     | 1  | 48          | 1  | 48         | 1.2%       |
| Khoo 2007        | 1  | 35          | 3  | 35         | 3.7%       |
| Lemenu 2012      | 2  | 40          | 2  | 38         | 2.5%       |
| Muller 2009      | 1  | 76          | 2  | 75         | 2.5%       |
| Ren 2012         | 5  | 299         | 5  | 298        | 6.1%       |
| van Bree 2011    | 1  | 36          | 1  | 36         | 1.2%       |
| Veenhof 2012     | 2  | 36          | 4  | 43         | 4.5%       |
| Vlug 2011        | 15 | 193         | 13 | 207        | 15.4%      |
| Wang 2011        | 4  | 106         | 2  | 104        | 2.5%       |
| **Subtotal (95%CI)** |   |   |        | 0.92 (0.60, 1.43) | |
|                   | 36 | 40          |        |            |            |
| **Total events** |     |             |        |            |            |

Heterogeneity: $\chi^2 = 3.68, df = 10 (P = 0.96); I^2 = 0$
Test for overall effect: $Z = 0.36 (P = 0.72)$

1.2.2 OFT vs OCC
| Study or subgroup | Events | Total Events | Weight | Risk ratio | Risk ratio |
|------------------|--------|--------------|--------|------------|------------|
| García-Botello 2011 | 4 | 61          | 6 | 58         | 7.5%       |
| Hübner 2010      | 0 | 36          | 1 | 31         | 2.0%       |
| Lonescu 2009     | 1 | 48          | 1 | 48         | 1.2%       |
| Khoo 2007        | 1 | 35          | 3 | 35         | 3.7%       |
| Muller 2009      | 1 | 76          | 2 | 75         | 2.5%       |
| Ren 2012         | 5 | 299         | 5 | 298        | 6.1%       |
| van Bree 2011    | 1 | 36          | 1 | 36         | 1.2%       |
| Veenhof 2012     | 2 | 36          | 4 | 43         | 4.5%       |
| Vlug 2011        | 15 | 193        | 13 | 207        | 15.4%      |
| Vlug 2011        | 2 | 17          | 1 | 20         | 1.1%       |
| **Subtotal (95%CI)** | 683 | 681 | 33.1% | 0.90 (0.53, 1.53) | |
|                   | 23 | 26          |        |            |            |
| **Total events** |     |             |        |            |            |

Heterogeneity: $\chi^2 = 3.44, df = 8 (P = 0.90); I^2 = 0$
Test for overall effect: $Z = 0.40 (P = 0.69)$

1.2.3 LFT vs LCC
| Study or subgroup | Events | Total Events | Weight | Risk ratio | Risk ratio |
|------------------|--------|--------------|--------|------------|------------|
| Lemanu 2012      | 2 | 40          | 2 | 38         | 2.5%       |
| van Bree 2011    | 0 | 18          | 1 | 18         | 1.8%       |
| Veenhof 2012     | 2 | 17          | 1 | 20         | 1.1%       |
| Vlug 2011        | 8 | 93          | 7 | 98         | 8.4%       |
| **Subtotal (95%CI)** | 283 | 292 | 17.8% | 0.98 (0.48, 2.01) | |
|                   | 13 | 14          |        |            |            |
| **Total events** |     |             |        |            |            |

Heterogeneity: $\chi^2 = 2.73, df = 4 (P = 0.60); I^2 = 0$
Test for overall effect: $Z = 0.05 (P = 0.96)$

Total (95%CI) | 1932 | 1946 | 100.0% | 0.93 (0.68, 1.25) |
Total events | 72 | 80 |

Heterogeneity: $\chi^2 = 9.95, df = 24 (P = 0.99); I^2 = 0$
Test for overall effect: $Z = 0.50 (P = 0.62)$

Favours experimental Favours control
| Study or subgroup | Events FT | Total FT | Events CC | Total CC | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-----------|----------|-----------|----------|--------|-----------------------------|-----------------------------|
| **1.3.1 FT vs CC** |           |          |           |          |        |                             |                             |
| Anderson 2003    | 1         | 14       | 1         | 11       | 1.1%   | 0.79 (0.06, 11.20)          |                             |
| García-Botello 2011 | 12      | 61       | 11        | 58       | 11.2%  | 1.04 (0.50, 2.16)           |                             |
| Gatt 2005        | 3         | 19       | 3         | 20       | 2.9%   | 1.05 (0.24, 4.59)           |                             |
| Muller 2009      | 3         | 76       | 4         | 75       | 4.0%   | 0.74 (0.17, 3.20)           |                             |
| Ren 2012         | 6         | 299      | 7         | 298      | 7.0%   | 0.85 (0.29, 2.51)           |                             |
| Veenhof 2012     | 4         | 36       | 4         | 43       | 3.6%   | 1.19 (0.32, 4.44)           |                             |
| Vlug 2011        | 12        | 193      | 13        | 207      | 12.5%  | 0.99 (0.46, 2.12)           |                             |
| Wang 2011        | 2         | 106      | 5         | 104      | 5.0%   | 0.39 (0.08, 1.98)           |                             |
| Wang 2011        | 0         | 40       | 2         | 38       | 2.6%   | 0.19 (0.01, 3.84)           |                             |
| **Subtotal (95%CI)** | 844 | 854 | 50.0% | | | 0.87 (0.59, 1.29) | |
| **Total events** | 43        | 50       |           |          |        |                             |                             |

Heterogeneity: $\chi^2 = 2.58$, df = 8 ($P = 0.96$); $I^2 = 0$
Test for overall effect: $Z = 0.68$ ($P = 0.50$)

| Study or subgroup | Events FT | Total FT | Events CC | Total CC | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-----------|----------|-----------|----------|--------|-----------------------------|-----------------------------|
| **1.3.2 OFT vs OCC** |           |          |           |          |        |                             |                             |
| Anderson 2003    | 1         | 14       | 1         | 11       | 1.1%   | 0.79 (0.06, 11.20)          |                             |
| García-Botello 2011 | 12      | 61       | 11        | 58       | 11.2%  | 1.04 (0.50, 2.16)           |                             |
| Gatt 2005        | 3         | 19       | 3         | 20       | 2.9%   | 1.05 (0.24, 4.59)           |                             |
| Muller 2009      | 3         | 76       | 4         | 75       | 4.0%   | 0.74 (0.17, 3.20)           |                             |
| Ren 2012         | 6         | 299      | 7         | 298      | 7.0%   | 0.85 (0.29, 2.51)           |                             |
| Veenhof 2012     | 3         | 17       | 3         | 20       | 2.7%   | 1.18 (0.27, 5.09)           |                             |
| Vlug 2011        | 5         | 93       | 5         | 98       | 4.9%   | 1.05 (0.32, 3.52)           |                             |
| **Subtotal (95%CI)** | 579 | 581 | 33.9% | | | 0.97 (0.62, 1.52) | |
| **Total events** | 33        | 34       |           |          |        |                             |                             |

Heterogeneity: $\chi^2 = 0.33$, df = 6 ($P = 1.00$); $I^2 = 0$
Test for overall effect: $Z = 0.13$ ($P = 0.90$)

| Study or subgroup | Events FT | Total FT | Events CC | Total CC | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-----------|----------|-----------|----------|--------|-----------------------------|-----------------------------|
| **1.3.3 LFT vs LCC** |           |          |           |          |        |                             |                             |
| Veenhof 2012     | 1         | 19       | 1         | 23       | 0.9%   | 1.21 (0.08, 18.09)          |                             |
| Vlug 2011        | 7         | 100      | 8         | 109      | 7.6%   | 0.95 (0.36, 2.53)           |                             |
| Wang 2011        | 2         | 106      | 5         | 104      | 5.0%   | 0.39 (0.08, 1.98)           |                             |
| Wang 2011        | 0         | 40       | 2         | 38       | 2.6%   | 0.19 (0.01, 3.84)           |                             |
| **Subtotal (95%CI)** | 265 | 274 | 16.1% | | | 0.67 (0.32, 1.42) | |
| **Total events** | 10        | 16       |           |          |        |                             |                             |

Heterogeneity: $\chi^2 = 1.78$, df = 3 ($P = 0.62$); $I^2 = 0$
Test for overall effect: $Z = 1.04$ ($P = 0.30$)

| Study or subgroup | Events FT | Total FT | Events CC | Total CC | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-----------|----------|-----------|----------|--------|-----------------------------|-----------------------------|
| **Total (95%CI)** | 1688      | 1709     | 100.0%    |          |        | 0.87 (0.67, 1.15)           |                             |
| **Total events** | 86        | 100      |           |          |        |                             |                             |

Heterogeneity: $\chi^2 = 5.17$, df = 19 ($P = 1.00$); $I^2 = 0$
Test for overall effect: $Z = 0.96$ ($P = 0.34$)

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## Risk ratio

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI | M-H, fixed, 95%CI |
|------------------|--------|-------|--------|-------|--------|-------------------|-------------------|
| **1.4.1 FT vs CC** |        |       |        |       |        |                   |                   |
| Anderson 2003    | 1      | 14    | 0      | 11    | 0.3%   | 2.40 (0.11, 53.77) |                   |
| García-Botello 2011 | 9      | 51   | 12     | 58    | 7.1%   | 0.71 (0.32, 1.56)  |                   |
| Gatt 2005        | 0      | 19    | 4      | 20    | 2.5%   | 0.12 (0.01, 2.03)  |                   |
| Hu 2012          | 1      | 40    | 4      | 42    | 2.2%   | 0.26 (0.03, 2.25)  |                   |
| Lonescu 2009     | 4      | 48    | 5      | 48    | 2.9%   | 0.80 (0.23, 2.80)  |                   |
| Muller 2009      | 4      | 76    | 7      | 75    | 4.0%   | 0.56 (0.17, 1.85)  |                   |
| Ren 2012         | 5      | 299   | 5      | 298   | 2.9%   | 1.00 (0.29, 3.41)  |                   |
| Serclova 2009    | 4      | 51    | 17     | 52    | 9.6%   | 0.24 (0.09, 0.66)  |                   |
| Veenhof 2012     | 3      | 36    | 2      | 43    | 1.0%   | 1.79 (0.32, 10.14) |                   |
| Vlug 2011        | 22     | 193   | 18     | 207   | 10.0%  | 1.31 (0.73, 2.37)  |                   |
| Wang 2010        | 2      | 47    | 1      | 49    | 0.6%   | 0.98 (0.51, 1.89)  |                   |
| Wang 2011        | 4      | 48    | 5      | 53    | 2.9%   | 0.74 (0.22, 2.47)  |                   |
| **Total (95%CI)** | 1062   | 1071  | 50.1%  | 50.1% | 0.72 (0.52, 0.97)  |                   |
| **Total events** | 61     | 67    |        |       |        |                   |                   |
| **Heterogeneity:** |        |       |        |       |        | $\chi^2 = 14.43$, df = 13 ($P = 0.34$); $I^2 = 10\%$ |
| **Test for overall effect:** | Z = 2.13 ($P = 0.03$) |

## Risk ratio

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI | M-H, fixed, 95%CI |
|------------------|--------|-------|--------|-------|--------|-------------------|-------------------|
| **1.4.2 OFT vs OCC** |        |       |        |       |        |                   |                   |
| Anderson 2003    | 1      | 14    | 0      | 11    | 0.3%   | 2.40 (0.11, 53.77) |                   |
| García-Botello 2011 | 9      | 61   | 12     | 58    | 7.1%   | 0.71 (0.32, 1.56)  |                   |
| Gatt 2005        | 0      | 19    | 4      | 20    | 2.5%   | 0.12 (0.01, 2.03)  |                   |
| Hu 2012          | 1      | 21    | 3      | 20    | 1.8%   | 0.32 (0.04, 2.80)  |                   |
| Lonescu 2009     | 4      | 48    | 5      | 48    | 2.9%   | 0.80 (0.23, 2.80)  |                   |
| Muller 2009      | 4      | 76    | 7      | 75    | 4.0%   | 0.56 (0.17, 1.85)  |                   |
| Ren 2012         | 5      | 299   | 5      | 298   | 2.9%   | 1.00 (0.29, 3.41)  |                   |
| Serclova 2009    | 4      | 51    | 17     | 52    | 9.6%   | 0.24 (0.09, 0.66)  |                   |
| Veenhof 2012     | 3      | 36    | 2      | 43    | 1.0%   | 1.79 (0.32, 10.14) |                   |
| Vlug 2011        | 22     | 193   | 18     | 207   | 10.0%  | 1.31 (0.73, 2.37)  |                   |
| Wang 2010        | 2      | 47    | 1      | 47    | 0.6%   | 0.98 (0.51, 1.89)  |                   |
| Wang 2011        | 4      | 48    | 5      | 53    | 2.9%   | 0.12 (0.01, 2.03)  |                   |
| **Total (95%CI)** | 731    | 730   | 38.4%  | 38.4% | 0.72 (0.51, 1.02)  |                   |
| **Total events** | 47     | 66    |        |       |        |                   |                   |
| **Heterogeneity:** |        |       |        |       |        | $\chi^2 = 13.87$, df = 10 ($P = 0.18$); $I^2 = 28\%$ |
| **Test for overall effect:** | Z = 1.85 ($P = 0.06$) |

## Risk ratio

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI | M-H, fixed, 95%CI |
|------------------|--------|-------|--------|-------|--------|-------------------|-------------------|
| **1.4.3 LFT vs LCC** |        |       |        |       |        |                   |                   |
| Chen Hu 2012     | 0      | 19    | 1      | 22    | 0.8%   | 0.38 (0.02, 0.88)  |                   |
| Veenhof 2012     | 1      | 19    | 1      | 23    | 0.5%   | 1.21 (0.08, 18.09) |                   |
| Vlug 2011        | 6      | 100   | 8      | 109   | 4.4%   | 0.82 (0.29, 2.27)  |                   |
| Wang 2011        | 1      | 106   | 7      | 104   | 4.0%   | 0.56 (0.17, 1.86)  |                   |
| Wang 2011        | 1      | 40    | 3      | 38    | 1.8%   | 0.32 (0.03, 2.91)  |                   |
| **Total (95%CI)** | 284    | 296   | 11.5%  | 11.5% | 0.64 (0.32, 1.26)  |                   |
| **Total events** | 12     | 20    |        |       |        |                   |                   |
| **Heterogeneity:** |        |       |        |       |        | $\chi^2 = 0.97$, df = 4 ($P = 0.91$); $I^2 = 0\%$ |
| **Test for overall effect:** | Z = 1.29 ($P = 0.20$) |

## Risk ratio

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI | M-H, fixed, 95%CI |
|------------------|--------|-------|--------|-------|--------|-------------------|-------------------|
| **Total (95%CI)** | 2077   | 2097  | 100.0% | 100.0%| 0.71 (0.57, 0.88)  |                   |
| **Total events** | 120    | 173   |        |       |        |                   |                   |
| **Heterogeneity:** |        |       |        |       |        | $\chi^2 = 29.43$, df = 29 ($P = 0.44$); $I^2 = 1\%$ |
| **Test for overall effect:** | Z = 3.09 ($P = 0.002$) |

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TF: Fast-track rehabilitation; CC: Control; FT: Fast-track rehabilitation for gastrointestinal malignancy; OFT: Observation fast-track rehabilitation; OCC: Observation control; LFT: Low fast-track rehabilitation; LCC: Low control; D: Data.
| Study or subgroup | FT Events | Total | Events | Total | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|-----------|-------|--------|-------|--------|--------------------------------|--------------------------------|
| 1.5.1 FT vs CC   | 3         | 61    | 2      | 58    | 1.9%   | 1.43 (0.25, 8.23)             |                                 |
| García-Botello 2011 | 1         | 19    | 4      | 20    | 3.7%   | 0.26 (0.03, 2.15)             |                                 |
| Khoo 2007        | 3         | 35    | 1      | 35    | 0.9%   | 3.00 (0.33, 27.46)            |                                 |
| Lemanu 2012      | 8         | 40    | 8      | 38    | 7.7%   | 0.95 (0.40, 2.28)             |                                 |
| Muller 2009      | 3         | 76    | 2      | 75    | 1.9%   | 1.48 (0.25, 8.61)             |                                 |
| Srinivasa 2013   | 9         | 37    | 4      | 37    | 3.8%   | 2.25 (0.76, 6.67)             |                                 |
| van Bree 2011    | 9         | 36    | 12     | 36    | 11.3%  | 0.75 (0.36, 1.56)             |                                 |
| Vlug 2011        | 13        | 193   | 14     | 207   | 12.7%  | 1.00 (0.48, 2.06)             |                                 |
| Wang 2010        | 1         | 47    | 1      | 45    | 1.0%   | 0.96 (0.06, 14.85)            |                                 |
| Wang 2011        | 4         | 106   | 6      | 104   | 5.7%   | 0.65 (0.19, 2.25)             |                                 |
| Yang 2012        | 4         | 81    | 5      | 82    | 4.7%   | 0.81 (0.23, 2.91)             |                                 |
| **Subtotal (95%CI)** | 731      | 737   |        |       | 55.2%  | 0.99 (0.71, 1.39)             |                                 |
| **Total events** | 58        | 59    |        |       |        |                                |                                 |

Heterogeneity: $\chi^2 = 6.15$, df = 10 ($P = 0.08$); $I^2 = 10$
Test for overall effect: $Z = 0.06$ ($P = 0.95$)

1.5.2 OFT vs OCC

| Study or subgroup | OFT Events | Total | Events | Total | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|------------|-------|--------|-------|--------|--------------------------------|--------------------------------|
| García-Botello 2011 | 3         | 61    | 2      | 58    | 1.9%   | 1.43 (0.25, 8.23)             |                                 |
| Gatt 2005        | 1         | 19    | 4      | 20    | 3.7%   | 0.26 (0.03, 2.15)             |                                 |
| Muller 2009      | 3         | 76    | 2      | 75    | 1.9%   | 1.48 (0.25, 8.61)             |                                 |
| van Bree 2011    | 1         | 18    | 2      | 18    | 1.9%   | 0.50 (0.05, 5.04)             |                                 |
| Vlug 2011        | 7         | 93    | 7      | 98    | 6.4%   | 1.05 (0.38, 2.89)             |                                 |
| Wang 2010        | 1         | 47    | 1      | 45    | 1.0%   | 0.96 (0.06, 14.85)            |                                 |
| Wang 2012        | 3         | 41    | 2      | 42    | 1.9%   | 1.54 (0.27, 8.73)             |                                 |
| **Subtotal (95%CI)** | 390      | 391   |        |       | 19.5%  | 1.07 (0.60, 1.91)             |                                 |
| **Total events** | 22        | 21    |        |       |        |                                |                                 |

Heterogeneity: $\chi^2 = 3.37$, df = 7 ($P = 0.85$); $I^2 = 0$
Test for overall effect: $Z = 0.21$ ($P = 0.83$)

1.5.3 LFT vs LCC

| Study or subgroup | LFT Events | Total | Events | Total | Weight | Risk ratio M-H, fixed, 95%CI | Risk ratio M-H, fixed, 95%CI |
|------------------|------------|-------|--------|-------|--------|--------------------------------|--------------------------------|
| Lemanu 2012      | 8         | 40    | 8      | 38    | 7.7%   | 0.95 (0.40, 2.28)             |                                 |
| van Bree 2011    | 1         | 18    | 3      | 18    | 2.8%   | 0.33 (0.04, 2.91)             |                                 |
| Vlug 2011        | 6         | 100   | 7      | 109   | 6.3%   | 0.93 (0.32, 2.69)             |                                 |
| Wang 2011        | 4         | 106   | 6      | 104   | 5.7%   | 0.65 (0.19, 2.25)             |                                 |
| Wang 2012        | 1         | 40    | 3      | 40    | 2.8%   | 0.33 (0.04, 3.07)             |                                 |
| **Subtotal (95%CI)** | 304      | 309   |        |       | 25.3%  | 0.74 (0.43, 1.28)             |                                 |
| **Total events** | 20        | 27    |        |       |        |                                |                                 |

Heterogeneity: $\chi^2 = 1.55$, df = 4 ($P = 0.82$); $I^2 = 0$
Test for overall effect: $Z = 1.07$ ($P = 0.29$)

| Total (95%CI)   | 1425       | 1437   | 100.0%  |       | 0.94 (0.73, 1.22)             |                                 |
| **Total events** | 100        | 107    |        |       |        |                                |                                 |

Heterogeneity: $\chi^2 = 11.83$, df = 23 ($P = 0.97$); $I^2 = 0$
Test for overall effect: $Z = 0.45$ ($P = 0.65$)
### 4.1.1 complications

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI |
|-------------------|--------|-------|--------|-------|--------|------------------|
| Basse 2005        | 9      | 30    | 8      | 30    | 4.3%   | 1.13 (0.50, 2.52) |
| Chen Hu 2012      | 7      | 19    | 7      | 21    | 3.6%   | 1.11 (0.46, 2.57) |
| King 2008         | 6      | 41    | 5      | 19    | 3.7%   | 0.56 (0.19, 1.60) |
| Mackay 2006       | 6      | 22    | 13     | 58    | 3.9%   | 1.22 (0.53, 2.80) |
| van Bree 2011     | 3      | 18    | 10     | 18    | 5.4%   | 0.30 (0.10, 0.91) |
| Veenhof 2012      | 2      | 19    | 8      | 17    | 4.6%   | 0.22 (0.05, 0.91) |
| Vlug 2011         | 34     | 100   | 43     | 93    | 24.1%  | 0.74 (0.52, 1.04) |
| Wang 2012         | 2      | 40    | 4      | 41    | 2.1%   | 0.51 (0.10, 2.64) |
| Subtotal (95%CI)  | 289    | 297   | 51.7%  |       |        | 0.72 (0.56, 0.92) |

Total events = 69

Heterogeneity: $\chi^2 = 9.16$, df = 7 ($P = 0.24$); $I^2 = 24$

Test for overall effect: $Z = 2.57$ ($P = 0.01$)

### 4.1.2 anastomotic leak

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI |
|-------------------|--------|-------|--------|-------|--------|------------------|
| Basse 2005        | 1      | 30    | 0      | 30    | 0.3%   | 3.00 (0.13, 70.83) |
| Faiz 2008         | 6      | 191   | 1      | 50    | 0.9%   | 1.57 (0.19, 12.75) |
| King 2008         | 1      | 41    | 0      | 19    | 0.4%   | 1.43 (0.06, 33.54) |
| van Bree 2011     | 0      | 18    | 1      | 18    | 0.8%   | 0.33 (0.01, 7.68)  |
| Veenhof 2012      | 0      | 19    | 2      | 17    | 1.4%   | 0.18 (0.01, 3.50)  |
| Vlug 2011         | 7      | 100   | 8      | 93    | 4.5%   | 0.81 (0.31, 2.16)  |
| Subtotal (95%CI)  | 399    | 227   | 8.2%   |       |        | 0.83 (0.40, 1.73)  |

Total events = 15

Heterogeneity: $\chi^2 = 2.45$, df = 5 ($P = 0.78$); $I^2 = 0$

Test for overall effect: $Z = 0.48$ ($P = 0.63$)

### 4.1.3 wound infection

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI |
|-------------------|--------|-------|--------|-------|--------|------------------|
| Basse 2005        | 4      | 30    | 1      | 30    | 0.5%   | 4.00 (0.47, 33.73) |
| Chen Hu 2012      | 0      | 19    | 2      | 21    | 1.3%   | 0.22 (0.01, 4.31)  |
| Veenhof 2012      | 6      | 100   | 16     | 93    | 9.0%   | 0.35 (0.14, 0.85)  |
| Subtotal (95%CI)  | 168    | 161   | 11.9%  |       |        | 0.51 (0.26, 1.01)  |

Total events = 11

Heterogeneity: $\chi^2 = 4.60$, df = 3 ($P = 0.20$); $I^2 = 35$

Test for overall effect: $Z = 1.93$ ($P = 0.05$)

### 4.1.4 obstruction

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI |
|-------------------|--------|-------|--------|-------|--------|------------------|
| Basse 2005        | 2      | 30    | 0      | 30    | 0.3%   | 5.00 (0.25, 99.95) |
| Veenhof 2012      | 1      | 19    | 3      | 23    | 1.5%   | 0.40 (0.05, 3.57)  |
| Vlug 2011         | 7      | 100   | 5      | 93    | 2.8%   | 1.30 (0.43, 3.96)  |
| Subtotal (95%CI)  | 149    | 146   | 4.5%   |       |        | 1.23 (0.51, 3.00)  |

Total events = 10

Heterogeneity: $\chi^2 = 1.86$, df = 2 ($P = 0.40$); $I^2 = 0$

Test for overall effect: $Z = 0.46$ ($P = 0.65$)

### 4.1.5 re-admission

| Study or subgroup | Events | Total | Events | Total | Weight | M-H, fixed, 95%CI |
|-------------------|--------|-------|--------|-------|--------|------------------|
| Basse 2005        | 6      | 30    | 8      | 30    | 4.3%   | 0.75 (0.30, 1.90) |
| Faiz 2008         | 11     | 191   | 11     | 50    | 9.4%   | 0.26 (0.12, 0.57) |
| King 2008         | 2      | 41    | 5      | 19    | 3.7%   | 0.19 (0.04, 0.87) |
| van Bree 2011     | 1      | 18    | 1      | 18    | 0.5%   | 1.00 (0.07, 14.79) |
| Vlug 2011         | 6      | 100   | 7      | 93    | 3.9%   | 0.80 (0.28, 2.29)  |
| Wang 2012         | 1      | 40    | 3      | 41    | 1.6%   | 0.34 (0.04, 3.15)  |
| Subtotal (95%CI)  | 420    | 251   | 23.5%  |       |        | 0.45 (0.29, 0.71)  |

Total events = 27

Heterogeneity: $\chi^2 = 5.83$, df = 5 ($P = 0.32$); $I^2 = 14$

Test for overall effect: $Z = 3.41$ ($P < 0.0001$)

| Total (95%CI)     |       |       |       |       |        | 1425 | 1082 | 100.0% | 0.66 (0.54, 0.81) |
|-------------------|--------|-------|--------|-------|--------|------|------|--------|------------------|

Total events = 132

Heterogeneity: $\chi^2 = 30.19$, df = 26 ($P = 0.26$); $I^2 = 14$

Test for overall effect: $Z = 4.07$ ($P < 0.0001$)

### Figure 2

Forest plot of comparison. A: Complications; B: Anastomotic leak; C: Obstruction; D: Wound infection; E: Re-admission; F: LFT vs OFT. RRs are shown with 95% CIs.
\( \chi^2 = 2.45 \) (\( P = 0.78 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

**Wound infection:** Compared with CC, FT reduced wound infection. The pooled RR was 0.71 (95%CI: 0.57-0.88, \( P < 0.001 \)), \( \chi^2 = 29.43 \) (\( P = 0.44 \)) and \( I^2 = 1\% \) (Figure 2C, Table 3).

Fourteen studies (2133 patients) provided data on wound infection for FT vs CC; 5.7% (61/1062 patients) had wound infection in the FT group and 8.1% (87/1071) in the CC group. Pooling the results indicated that FT did not significantly reduce wound infection compared with CC. The WMD was 0.72 (95%CI: 0.52-0.97, \( P < 0.05 \)), \( \chi^2 = 14.43 \) (\( P = 0.34 \)) and \( I^2 = 10\% \), which excludes heterogeneity among the studies.

Twelve studies (1461 patients) provided data on wound infection for OFT vs OCC; 6.5% (47/731 patients) had wound infection in the OFT group and 9.0% (66/730) in the OCC group. Pooling the results indicated that OFT did not significantly reduce wound infection compared with OCC. The WMD was 0.72 (95%CI: 0.51-1.02, \( P > 0.05 \)), \( \chi^2 = 13.87 \) (\( P = 0.18 \)) and \( I^2 = 28\% \), which excludes heterogeneity among the studies.

Five studies (580 patients) provided data on wound infection for LFT vs LCC; 4.2% (12/284 patients) had wound infection in the LFT group and 6.8% (20/296) in the LCC group. Pooling the results indicated that LFT did not significantly reduce wound infection compared with LCC. The WMD was 0.64 (95%CI: 0.32-1.26, \( P > 0.05 \)), \( \chi^2 = 0.97 \) (\( P = 0.91 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Four studies (329 patients) provided data on wound infection for LFT vs OFT; 6.5% (11/168 patients) had wound infection in the LFT group and 13% (21/161) in the OFT group. Pooling the results indicated that LFT significantly reduce wound infection compared with OFT. The WMD was 0.51 (95%CI: 0.26-1.01, \( P = 0.05 \)), \( \chi^2 = 4.6 \) (\( P = 0.20 \)) and \( I^2 = 35\% \), which excludes heterogeneity among the studies.

**Obstruction:** Compared with CC, FT reduced obstruction. The pooled RR was 0.87 (95%CI: 0.67-1.15, \( P > 0.05 \)), \( \chi^2 = 5.17 \) (\( P = 1.00 \)) and \( I^2 = 0\% \) (Figure 2D, Table 3).

Nine studies (1698 patients) provided data on obstruction for FT vs CC; 5.1% (43/844 patients) had obstruction in the FT group and 5.9% (50/854) in the CC group. Pooling the results indicated that FT did not significantly reduce obstruction compared with CC. The WMD was 0.87 (95%CI: 0.59-1.29, \( P = 0.05 \)), \( \chi^2 = 2.58 \) (\( P = 0.96 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Seven studies (1160 patients) provided data on obstruction for OFT vs OCC; 5.7% (33/579 patients) had obstruction in the OFT group and 5.9% (34/581) in the OCC group. Pooling the results indicated that OFT did not significantly reduce obstruction compared with OCC. The WMD was 0.97 (95%CI: 0.62-1.52, \( P > 0.05 \)), \( \chi^2 = 0.33 \) (\( P = 1.00 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Four studies (539 patients) provided data on obstruction for LFT vs LCC; 3.8% (10/265 patients) had obstruction in the LFT group and 5.8% (16/274) in the LCC group. Pooling the results indicated that LFT did not significantly reduce obstruction compared with LCC. The WMD was 0.67 (95%CI: 0.32-1.42, \( P > 0.05 \)), \( \chi^2 = 1.78 \) (\( P = 0.62 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Three studies (295 patients) provided data on obstruction for LFT vs OFT; 6.7% (10/149 patients) had obstruction in the LFT group and 5.5% (8/146) in the OFT group. Pooling the results indicated that LFT significantly reduce obstruction compared with OFT. The WMD was 1.23 (95%CI: 0.51-3.00, \( P > 0.05 \)), \( \chi^2 = 1.86 \) (\( P = 0.40 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

**Re-admission:** Compared with CC, FT reduced re-admission. The pooled RR was 0.94 (95%CI: 0.73-1.22, \( P > 0.05 \)), \( \chi^2 = 11.83 \) (\( P = 0.97 \)) and \( I^2 = 0\% \) (Figure 2E, Table 3).

Eleven studies (1468 patients) provided data on re-admission for FT vs CC; 7.9% (58/731 patients) had readmission in the FT group and 8% (59/737) in the CC group. Pooling the results indicated that FT did not significantly reduce re-admission compared with CC. The WMD was 0.99 (95%CI: 0.71-1.39, \( P = 0.05 \)), \( \chi^2 = 6.15 \) (\( P = 0.80 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Eight studies (781 patients) provided data on readmission for OFT vs OCC; 5.6% (22/390 patients) had re-admission in the OFT group and 5.4% (21/391) in the OCC group. Pooling the results indicated that OFT did not significantly reduce re-admission compared with OCC. The WMD was 1.07 (95%CI: 0.60-1.91, \( P > 0.05 \)), \( \chi^2 = 3.37 \) (\( P = 0.85 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Five studies (613 patients) provided data on re-admission for LFT vs LCC; 6.6% (20/304 patients) had re-admission in the LFT group and 8.7% (27/309) in the LCC group. Pooling the results indicated that LFT did not significantly reduce re-admission compared with LCC. The WMD was 0.74 (95%CI: 0.43-1.28, \( P > 0.05 \)), \( \chi^2 = 1.55 \) (\( P = 0.82 \)) and \( I^2 = 0\% \), which excludes heterogeneity among the studies.

Six studies (671 patients) provided data on re-admission for LFT vs OFT; 6.7% (27/420 patients) had re-admission in the LFT group and 5.5% (35/251) in the OFT group. Pooling the results indicated that LFT significantly reduced re-admission compared with OFT. The WMD was 0.45 (95%CI: 0.29-0.71, \( P < 0.001 \)), \( \chi^2 = 5.83 \) (\( P = 0.32 \)) and \( I^2 = 14\% \), which excludes heterogeneity among the studies.

**Publication bias**

A funnel plot was created to access the publication bias of the literature. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figures 2F and 3).
DISCUSSION

The present meta-analysis showed that compared with CC, FT reduced complications and re-admission, and had a similar probability of anastomotic leaks, wound infection and obstruction. Compared with OFT, LFT reduced complications and re-admission, the probability of anastomotic leaks, wound infection and obstruction are similar.

The safety of FT after gastrointestinal surgery has been discussed in worldwide. A recent multivariate analysis demonstrated that male sex, preoperative education, psychological counseling, anesthesia, early postoperative oral nutrition and quality of care were potential risk factors for complications after gastrointestinal surgery. In addition, some studies have found an increased risk of anastomotic leaks in men and 10.1% of the men required reoperation for anastomotic leak vs 3.3% of women.

Preoperative education and psychological counseling are crucial factors for FT. It is necessary to introduce the detailed treatment program, different steps of FT, and relevant measures, and ease the psychological pressure in order to help patients better understand and coordinate the FT.

Better cooperation of patients can bring better outcomes of FT. Generally, the gastric emptying time of solid meal and fluid is 6 h and 2 h, respectively. Moderate activity after surgery may enhance recover and reduce complications. The patients should be encouraged to have a liquid meal 2 h before the operation instead of fasting. It has been shown that preoperative oral carbohy-
The role of epidural or regional anesthesia in FT should be stressed. Postoperative epidural analgesia can avoid stress-induced neurological, endocrinological and homeostatic changes or the blocking of sympathetic nervous system-related surgical stress response, reduce postoperative complications such as nausea, vomiting and enteroparesis, increase early ambulation, improve intestinal function, and shorten hospital stay after resection of gastrointestinal cancer. 

Early postoperative oral nutrition is regarded as an essential part of FT. Food intake can stimulate gastrointestinal peristalsis, and early feeding during the first 24 h after surgery promotes recovery of obstruction. It has been illustrated that early postoperative oral nutrition attenuates catabolism and potentially decreases infectious complications.

FT can improve the rehabilitation of patients after resection of gastrointestinal cancer better than CC can, thus benefitting surgery, anesthesia, pain management, physical therapy, and social work. The primary work of FT is the preoperative education of patients to make them understand the whole plan and the aim of each stage. Therefore, it is necessary to obtain cooperation from nurses.

The pathophysiological mechanisms involved in postoperative obstruction are still not completely understood, but recent studies have stressed the importance of inflammation of the intestinal muscularis resulting from handling during surgery. The faster clinical recovery observed after laparoscopic surgery compared with open surgery could be explained by decreased tissue trauma with concomitantly decreased mast cell activation, leading to attenuated intestinal inflammation and thus quicker gastrointestinal recovery. The mechanisms behind the beneficial effect of FT remain unclear.

Several cytokines, such as IL-6, TNF-α and CRP, are involved in the response to surgical stress and are therefore useful serum markers for evaluating the severity of surgery-induced stress. CRP is a nonspecific acute phase protein produced by the liver following trauma or inflammation. Serum CRP level is closely associated with trauma and stress; therefore, measurement of postoperative CRP may reflect the degree of trauma caused by a surgical procedure. The CRP level after colon surgery with LFT was significantly lower than that after other strategies, demonstrating that LFT is less traumatic for patients and reduces stress in the perioperative period, protecting the postoperative immune system. IL-6 is produced and activated by monocytes, macrophages and endothelial cells under conditions of surgical trauma and stress. IL-6 levels are positively correlated with the severity of surgical trauma. The increase in serum IL-6 was less after colon surgery with LFT, suggesting that a suitable surgical mode combined with better perioperative care can lead to less surgical trauma and better prognosis. Surgical trauma causes marked metabolic changes, and REE also acts as the marker for surgical stress. The REE rate of patients from the FT group was lower than that in the conventional surgery group, particularly on postoperative days 1 and 3.

Postsurgical complications in patients who underwent FT for colorectal diseases were treated without specific side effects or complications. Compared with CC, FT greatly reduced complications, and no other side effects were found. FT is safe and feasible. Compared with OFT, LTF significantly reduced complications, in addition to reducing hospitalization time and improving quality of life. LFT is not yet practiced widely, but we believe that it will become increasingly popular. Further large studies with more stringent quality criteria may improve the statistical power and confirm that LFT programs reduce morbidity and promote recovery. We believe that FT is significantly advantageous over other procedures for patients after resection of gastrointestinal malignant disease.

There have been eight previous systematic reviews, including meta-analyses on this topic. These included three reviews of controlled clinical trials and RCTs, and five reviews of RCTs only. The present study is the first meta-analysis to have compared FT vs CC or OFT vs OCC or LFT vs LCC or LFT vs OFT in resection for gastrointestinal malignancy, and the first meta-analysis of patients undergoing elective gastrointestinal surgery to demonstrate that FT is associated with a significant reduction in postoperative complications but not re-admission rates. The quality of evidence from the present study was supported by the increased number of included studies. In our study, reports from all trials had previously been subject to external peer review, and the risk of bias in these trials for the outcomes of interest was judged to be low in our assessments (Table 2).

There were several limitations to the present meta-analysis. First, the sample size of some of the studies was low, as was the number of studies included in our meta-analysis. Data extraction and analyses were not blinded to the authors, journals or institutions of the publications; however, the literature screening and data extraction were conducted independently by two investigators, and thus, the selection bias was unlikely. Second, the funnel plots were asymmetrical for some outcomes, which indicated the existence of publication bias. However, other factors such as study size and clinical and statistical heterogeneity may also cause an asymmetric funnel in the present meta-analysis. Finally, the included studies did not adequately evaluate hospital costs and quality of life after surgery, which are important outcomes for patients undergoing elective colorectal surgery.

In conclusion, this study provides a more detailed assessment of the potential effects of FT than has previously been possible. We were unable to confirm the large proportional reduction in risk suggested by some previous studies. However, more modest but perhaps clinically worthwhile reduction of complications in some or all types of patient cannot be ruled out. Implementation of FT and the maintenance of compliance may require collaboration and communication between dietitians, nurses, surgeons, anesthesiologists, and patients. Additional RCTs...
of FT with long-term follow-up are necessary to assess hospital costs and quality of life after surgery. Future studies may assess the benefits of FT in elderly patients and patients having other gastrointestinal surgery.

**COMMENTS**

**Background**

Fast-track rehabilitation protocols (FP) have become the most fashionable method of treatment for gastrointestinal malignancy. Complications of FP after gastrointestinal resection have been discussed in China as well as other countries.

**Research frontiers**

Over the past three decades, many studies have assessed the performance of FT. However, comparisons of FT and conventional care strategies (CC) or FT and laparoscopic surgery and FT and open surgery after gastrointestinal surgery have not been published.

**Innovations and breakthroughs**

Based on this meta-analysis, FT for gastrointestinal malignancy is safe and efficacious. Similar associations were indicated in subgroup analyses of East Asian, Western, cohort, and high-quality studies. These findings were not presented clearly in previous systematic reviews.

**Applications**

FT appears to be neither directly nor indirectly associated with the risk. Further studies should seek to clarify this conclusion.

**Peer review**

FT is rapidly becoming the focal point of attraction for specialists worldwide. This article shows the advantages of the procedure. This analysis has great practical value for clinicians.
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