Does lateral lymph node dissection for low rectal cancer improve overall survival? Protocol for a systematic review and meta-analysis

Jeremy Meyer a,⇑, Niki Christou b, Christophe Combescure c, Nicolas Buchs a, Frédéric Ris a

a Division of Digestive Surgery, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland
b Service de chirurgie digestive, endocrinienne et générale, CHU de Limoges, Limoges Cedex 87042, France
c Division of Clinical Epidemiology, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland

1. Introduction

Nowadays, total mesorectal excision constitutes the gold standard to remove perirectal lymph nodes [2]. However, in advanced cases, the lymphatic spread of mid to low rectal cancer proceeds further towards the origin of the inferior mesenteric artery and laterally alongside the internal iliac artery [3]. The incidence of metastasis to lateral lymph nodes was estimated to be of 10.8% [4]. Preoperative imaging might help identifying metastatic lateral lymph nodes [5]. To prevent cancer recurrence, lateral lymph nodes need to be treated with curative intent [6].

To this end, in patients with locally advanced rectal cancer whose lower tumor border is located distal to the peritoneal reflection, Japanese surgeons add lateral lymph node dissection to total mesorectal excision [7,8]. On the other side, Western surgeons, considering the morbidity associated with lateral lymph node dissection, associate preoperative radiochemotherapy to total mesorectal excision [2]. However, this strategy was demonstrated to be inefficient in preventing local recurrence in patients with cT3-4 rectal cancer and enlarged lymph nodes on preoperative imaging [9].

However, the choice of the procedure offering the best survival for patients with low rectal cancer remains poorly documented, especially in patients with enlarged lateral lymph nodes on preoperative imaging, and some authors advise to perform lateral lymph node dissection in these patients [10].

Therefore, our objective is to perform a systematic review and meta-analysis of the literature determining whether lateral lymph node dissection for low rectal cancer improves overall survival and recurrence-free survival.

2. Objective

The primary objective is to determine whether lateral lymph node dissection for low advanced rectal cancer improves overall survival compared to radiochemotherapy.
survival. The secondary objective is to determine whether lateral lymph node dissection for low rectal cancer improves recurrence-free survival in these patients.

3. Methods and analysis

This systematic review will be carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [1]. MEDLINE, Embase, Cochrane and Web of Science will be searched from inception to the 16th of January 2019 for original studies written in English or in French including patients who benefited from lateral lymph node dissection for low rectal cancer. Additional records will be identified by manual search of the reference lists of the included publications. Case series, conference abstracts, letters to the editor and secondary analyses of previously published papers will be excluded. Studies including patients with recurrent rectal cancer, pediatric population, patients undergoing multivisceral resection or studies without control group (without lateral lymph node dissection) will be excluded. Studies not reporting overall survival for patients with and without lateral lymph node dissection will be excluded.

Studies will be selected for inclusion using the Covidence software [11] by two authors (JM, NC). Discrepancies will be solved by a third author (FR). The following data will be extracted: first author, publication year, country where the investigation took place, study period, study design, number of patients included, number of patients who underwent lateral lymph node dissection, number of patients who did not undergo lateral lymph node dissection, number of male patients for each group, number of patients with metastatic lateral lymph nodes (among patients who underwent lateral lymph node dissection), number of patients who underwent preoperative radio- and/or chemotherapy for each group, type of neoadjuvant treatment in these patients, oncological stages of included patients for each group, overall survival for each group, recurrence-free survival for each group.

Hazard ratios (HR) of overall and recurrence-free survivals extracted from included will be combined using the method of the inverse of the variance (model with fixed effects) in absence of sensitive heterogeneity (I2 < 50%). In case of heterogeneity (I2 > 50%), a model with random effects will be used (Der Simonian and Laird’s approach [12]). In detail, the logarithm of HR will be combined and the standard errors of the logarithm of HR will be derived by dividing by 2*1.96 the width of the 95% confidence interval of logarithm of HR. The presence of heterogeneity will be investigated by applying Cochran’s Q test and by assessing the I2 statistic.

Two authors (JM, NC) will perform the critical appraisal of the included studies. Risk of bias will be assessed by using the Newcastle-Ottawa scale. Discrepancies will be solved by a third author (FR). Studies will be ranked as very good (8–10 points), good (6–8 points), satisfactory (4–6 points) or unsatisfactory (<4 points) for the studied outcome. Subgroup analyses will be performed by separately pooling studies according to their ranking on the Newcastle-Ottawa scale.

4. Conclusion

This systematic review and meta-analysis of the literature will help determining what is the best therapeutic strategy to treat lateral lymph node in patients with mid to low advanced rectal cancer.

Ethical approval

Ethical approval was not required.

Funding

None.

Author contribution

JM and CC designed the study. JM drafted the manuscript. JM, NC, CC, NC and FR performed critical revisions and accepted the final version of the manuscript.

Conflict of interest statement

No conflict of interest to declare.

Guarantor

Dr. Jeremy Meyer, MD, MD–PHD, Division of Digestive Surgery, University Hospitals of Geneva, Switzerland.Jeremy.meyer@hcuge.ch

Research registration number

The systematic review and meta-analysis protocol is registered on the International Prospective Register of Ongoing Systematic Reviews (PROSPERO) with number CRD42019123181.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.isjp.2019.09.001.

References

[1] D. Moher, A. Liberati, J. Tetzlaff, et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J. Clin. Epidemiol. 62 (2009) 1006–1012.
[2] C.J. van de Velde, P.G. Boelens, J.M. Borras, et al., EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum, Eur. J. Cancer 50 (1) (2014), e1–e34.
[3] K. Funahashi, J. Koike, M. Shimada, et al., A preliminary study of the draining lymph node basin in advanced lower rectal cancer using a radioactive tracer, Dis. Colon Rectum 49 (2006) 553–558.
[4] K.Y. Tam, S. Yamamoto, S. Fujita, et al., Improving prediction of lateral node spread in low rectal cancers–multivariate analysis of clinicopathological factors in 1,046 cases, Langenbecks Arch. Surg. 395 (2010) 545–549.
[5] T.H. Kim, S.Y. Jeong, D.H. Choi, et al., Lateral lymph node metastasis is a major cause of locoregional recurrence in rectal cancer treated with preoperative chemoradiotherapy and curative resection, Ann. Surg. Oncol. 15 (2008) 729–737.
[6] S. Manfredi, A.M. Benhamiche, B. Meny, et al., Population-based study of factors influencing occurrence and prognosis of local recurrence after surgery for rectal cancer, Br. J. Surg. 88 (2001) 1221–1227.
[7] T. Watanabe, K. Muro, Y. Ajioka, et al., Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer, Int. J. Clin. Oncol. 23 (2018) 1–34.
[8] S. Fujita, J. Mizusawa, Y. Kanemitsu, et al., Mesorectal excision with or without lateral lymph node dissection for clinical stage II/III lower rectal cancer (JCOG0212): a multicenter, randomized controlled, noninferiority trial, Ann. Surg. 265 (2017) 201–207.
[9] A. Ogura, T. Konishi, C. Cunningham, et al., Neoadjuvant (Chemo)radiotherapy with total mesorectal excision only is not sufficient to prevent local lateral recurrence in enlarged nodes: results of the multicenter lateral node study of patients with low cT3/4 rectal cancer, J. Clin. Oncol. 37 (2019) 33–43.
[10] M.J. Kim, J.H. Oh, Lateral lymph node dissection with the focus on indications, functional outcomes, and minimally invasive surgery, Ann. Coloproctol. 34 (2018) 229–233.
[11] https://www.covidence.org/reviews/active.
[12] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control Clin. Trials 7 (1986) 177–188.