Prognostic factors in rectal cancer: where is the evidence?

Les facteurs pronostiques du cancer du rectum: quels sont les niveaux de preuve ?

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RÉSUMÉ

survie à 5 ans du cancer du rectum est passée de 25% à près de 53 % tous stades confondus . Ce taux demeure encore faible, et ce malgré les progrès réalisés sur le plan diagnostique et thérapeutique.

Le but de notre travail était de répondre à la question : quels sont les facteurs pronostiques pré, per et post-opératoires du cancer du rectum, en se basant sur les règles de l'évidence-based medicine.

Méthodes : Nous avons réalisé une recherche bibliographique dans les bases dedonnées suivantes : Pubmed, Embase, Cochrane et Scopus. Les mots-clésutilisés étaient les suivants : «rectal cancer », « adenocarcinoma », « overallsurvival », « disease-free survival », « prognosis », « evidence-basedmedicine ». La survie globale à 5 ans a été retenue comme critère dejugement principal. La survie sans récidive a été retenue comme critère dejugement secondaire.Nous avons décidé de retenir les méta-analyses et les revues systématiquesdes essais cliniques ou de la littérature datant de moins de 6 ans.

Résultats : Nous avons retrouvé 270 publications, 27 articles répondant aux critères d'éligibilité sus-cités ont été retenus dans ce travail.Un volume opératoire élevé, la spécialisation en chirurgie colo-rectale,l'excision totale du mésorectum, une chimiothérapie adjuvante administréeau plus tard huit semaines après la chirurgie à vise curative, sont desfacteurs qui améliorent le pronostic dans le cancer du rectum avec un niveaul de preuve. Le lâchage anastomotique et le diabète aggravent le pronosticdu cancer du rectum avec un niveau I de preuve. Les marges de résection doivent être RO afin d'améliorer le pronostic du cancer du rectum avec un niveau I de preuve.

Conclusion: Les principaux facteurs pronostiques rapportés dans la littérature et qui doivent être retenus sont ceux sur lesquels le chirurgien peut agir, à savoir:le traitement néoadjuvant, le volume opératoire élevé, une ligature haute del'artère mésentérique inférieure, l'excision totale du mésorectum, la résection RO, l'amélioration des techniques de résection inter-sphinctérienne et des techniques anastomotiques ainsi qu'une chimiothérapie adjuvante qui doit être administrée au plus tard huit semaines après la résection si elle est indiquée.

Mots-clés

Cancer du rectum, pronostic, survie globale, survie sans récidive, evidence-based medicine.

SUMMARY

Background: In rectal cancer, the 5 years survival is about 53 % for all stages: it remains low in spite of the progress of diagnostic and therapeutic tools.

The aim of this work was to provide evidence based answers to the following question: what are the pre, intra and post operative prognostic factors in rectal cancer?

Methods: We have carried out a search in the following data bases: Pubmed, Embase, Cochrane and Scopus. The key words used were: « rectal cancer », « adenocarcinoma », « overall survival », « disease-free survival », « prognosis » and « evidence-based medicine ». The overall 5 years survival rate has been retained as primary outcome measure. Recurrence-free survival has been retained as secondary endpoint. Were included meta-analyses and systematic reviews of clinical trials dating back to less than six years.

Results: We retrieved 270 publications, 27 articles only met the above-mentioned eligibility criteria and thereof have been retained in this work. A high operating volume, a specialized surgeon in colorectal surgery, a total mesorectal excision, an adjuvant chemotherapy given within no more than 8 weeks following the curative resection improve prognosis in rectal cancer with level I of evidence. Anastomotic leak and diabetes worsen prognosis in rectal cancer with level I of evidence. Margin of surgical resection must be RO to improve prognosis in rectal cancer with level I of evidence.

Conclusion: The main prognostic factors found in literature which we should keep in mind are those on which surgeons can act: neoadjuvant treatment, high operating volume of the surgeon, high tie of the inferior mesenteric artery, mesorectal excision , RO resection, improvement of the techniques of intersphincteric resection and techniques of anastomosis and adjuvant chemotherapy within less than 8 weeks when appropriate.

Key-words

Rectal cancer, prognosis, overall survival, disease-free survival, evidence-based medicine.

Rectal cancer is the third digestive cancer in men [1]. The 5 years survival rate has increased from 25% to about 53 % for all stages [2-5]. This rate remains low in spite of the progress of diagnostic and therapeutic tools [5].
The aim of this work was to provide evidence based answers to the following question: what are the pre, intra and post operative prognostic factors in rectal cancer?

METHODS

We have carried out a search in the following data bases: Pubmed, Embase, Cochrane and Scopus. The key words used were: « rectal cancer », « adenocarcinoma », « overall survival », « disease-free survival », « prognosis » and « evidence-based medicine ». The overall 5 years survival rate has been retained as primary outcome measure. Recurrence-free survival has been retained as secondary endpoint.
Were included meta-analyses and systematic reviews of clinical trials dating back to less than six years. We used the structured abstracts of articles when their full-texts were not available or were available in other languages than english or french.
The full texts of all relevant abstracts were obtained and formally assessed for inclusion. We have decided to classify prognostic factors in three distinct groups: preoperative, intraoperative and postoperative prognostic factors.
The quality of randomized controlled trials (RCTs) was assessed using the Jadad scoring system [6]. The Methodological Index for Non-Randomized Studies (MINORS) index was used to assess the quality of non-randomized trials [7]. This index contains 12 items that are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The ideal global score is 24 for comparative studies and 16 for non-comparative studies. The quality of meta-analysis and systematic reviews of literature were evaluated with five criteria within the QUORUM statements [8] (table 1). All eligible studies were assessed for their methodology by W.D (table 2).
We considered in this review a randomized trial with sound methodology when Jadad score was ≥ 3, and for meta-analysis when Quorum score were ≥ 3 among the five mentioned criteria [6,8]. The Oxford classification has been used to assess the levels of evidence and the grade of recommendation [9].

Table 1 : Criteria of QUORUM statements (8) used to evaluate meta-analysis and systematic reviews

N°	Criteria of internal validity	yes/no
1	Identify the report as a meta-analysis of RCTs	yes/no
2	The information sources are reported in detail (databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)	yes/no
3	The validity assessment is reported (criteria and process used, quality assessment, and their findings)	yes/no
4	Report agreement on the selection and validity assessment	yes/no
5	The type of study design, participants' characteristics, details of intervention, outcome definitions, and how clinical heterogeneity were reported	yes/no

RESULTS

We retrieved 270 publications, 27 articles only met the above-mentioned eligibility criteria and thereof have been retained in this work (figure n°1).

1) Pre-operative prognostic factors

Diabetes

Diabetes has been studied in a meta-analysis which retained recurrence-free survival as secondary endpoint [10]. Diabetes reduces the recurrence-free survival [RR=1.54, 95% CI: 1.08-2.18] [10]. However, the authors concluded that the collected studies were heterogeneous and the median follow-up was short [10].

Table 2 : Characteristics of retained studies

Author	Type of study	Jadad Scale [6]	MINORS score [7]	QUORUM score [8]
MH et al., 2013 [10]	meta-analysis			3/5
Zhou et al., 2013 [11]	meta-analysis			3/5
Huang et al., 2011 [12]	prospective non-randomized		15/24	
Cocco et al., 2009 [13]	meta-analysis			4/5
Cocco et al., 2009 [14]	meta-analysis			4/5
Parma et al., 2010 [15]	meta-analysis			3/5
Leopaldi et al., 2010 [16]	meta-analysis			4/5
Lefevre et al., 2013 [21]	randomized controlled	3/5		
Zorcolo et al., 2012 [22]	meta-analysis			2/5
Martin et al., 2012 [23]	meta-analysis			3/5
Lee et al., 2013 [24]	meta-analysis			4/5
Archampong et al., 2012 [28]	retrospective (review)			4/5
Archampong et al., 2010 [25]	meta-analysis			4/5
Ohsaki et al., 2011 [27]	meta-analysis			4/5
Arezzo et al., 2013 [24]	meta-analysis			5/5

MINORS: Methodological Index for Non Randomized Studies

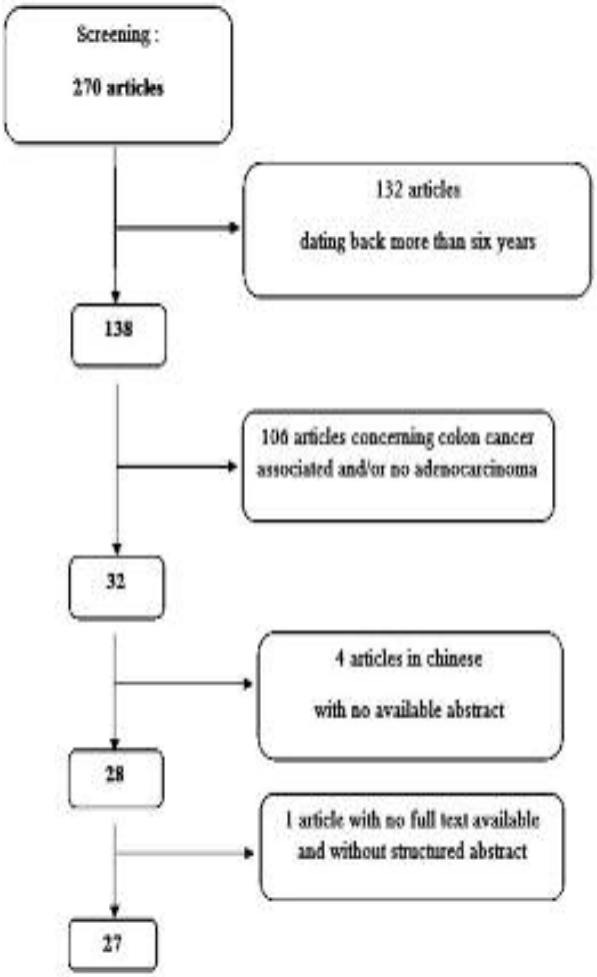

Figure 1: Flow chart showing screening process of relevant articles

Diabetes reduces the recurrence-free-survival in rectal cancer with level I of evidence.

Obesity

Zhou et al have studied in a meta-analysis the results of laparoscopic treatment of colorectal cancer in obese and non-obese people [11]. The authors concluded that there was no statistical significant difference regarding overall survival or recurrence-free survival at 2 years between, obese and non-obese patients. [11].

Obesity is not a prognostic factor in rectal cancer with level I of evidence.

Carcinoembryonic antigen (CEA)

CEA is an independent prognostic factor of overall survival when its rate is higher than 5ng/ml in rectal cancer with level II of evidence [12].

Neoadjuvant radiochemotherapy

Chemotherapy in addition to only radiation therapy in the rectal cancer stage II and stage III does not improve overall survival at 5 years (p=0.89) nor recurrence-free survival (p=0.79) according to a meta-analysis of Ceelen et al which included four randomized trials [13]. Ceelen et al have confirmed, in another meta-analysis which included 2336 patients, the same results for overall survival [OR=0.95, 95% CI: 0.79-1.14, p=0.15] and recurrence-free survival [OR=1.11, 95% CI: 0.92-1.34, p=0.64] [14].

In the same way, as concerns neoadjuvant radiochemothetrapy, the meta-analysis of Fiorica et al showed that adding chemotherapy to radiation did not have a statistically significant effect on overall survival at 5 years [RR=0.94, 95% CI: 0.94-1.09, p=0.68], but reduced the risk of local recurrence [RR=0.93, 95% CI : 0.90-0.96, p<0.001] [15].

Neoadjuvant radiochemotherapy does not improve the overall survival in rectal cancer with level I of evidence.

Neoadjuvant radiochemotherapy reduces the risk of local recurrence in rectal cancer with level I of evidence.

Targeted therapy

Adding a targeted bevacizumab therapy to a first-line chemotherapy improved overall survival [HR=0.78, 95% CI: 0.66-0.94, p=0.007] in metastatic rectal cancer according to the meta-analysis of Loupakis et al which included five randomized clinical trials and 2624 patients [16].

Targeted therapy added to first-line chemotherapy improves overall survival in metastatic rectal cancer with level I of evidence.

The time limit between the end of neoadjuvant radiochemotherapy and curative surgery

The time between the end of neoadjuvant radiochemotherapy and curative surgery has been suggested as a prognostic factor in rectal cancer [17-19]. Actually, the longer the delay (cut-off set at 8 weeks), the less local recurrence there was and the less distant metastases [20-21]. However, the impact of the delay between the end of neoadjuvant radiochemotherapy on overall survival at 5 years and recurrence-free survival has not been studied in literature, and is now the subject of a multi-center study of randomized trials (GRECCAR-6) [21]. The aim of this study is to compare two groups whose delay between the end of neoadjuvant treatment and surgery stood at 7 and 11 weeks respectively [21]. The secondary assessment criteria are overall survival and recurrence-free survival [21].

Curative surgery must occur at least 8 weeks after the end of radiochemotherapy in rectal cancer with level II of evidence.

Complete histological response after radiochemotherapy
The complete response after adjuvant radiochemotherapy improved overall survival at 5 years [OR=3.6, 95% CI: 1.84-7.22, p=0.002] and recurrence-free survival [OR=3.53, 95% CI: 1.62-7.72, p=0.002] according to the conclusions of Zorcolo's meta-analysis which included 1913 patients [22].
These results have been confirmed by Martin's meta-analysis which included 3363 patients [23]. This study concluded that overall survival at 5 years [OR=3,28, 95% CI: 1.66-6.51, p=0.001] and recurrence-free survival [OR=4.33, 95% CI: 2.31-8.09, p<0.001] were improved in patients who had a complete histological response versus those who had an incomplete response [23].
The complete response after adjuvant radiochemotherapy improves overall survival at 5 years and recurrence-free survival in rectal cancer with level II of evidence.

Partial histological response after radiochemotherapy
The partial response to neoadjuvant radiochemotherapy improved recurrence-free survival by about 50% [HR=0.49, 95% CI: 0.28-0.85] according to the meta-analysis of Lee et al with level I of evidence [24].
Other prognostic factors
Numerous other preoperative prognostic factors have also been found in literature, but clinical trials had few patients or a poor methodology. We will quote for example age, women, and the underprivileged social conditions [25-27].

2) Intra-operative prognostic factors

Surgeon's operating volume and surgeon's speciality
A high surgeon's operating volume [HR=0.85, 95% CI: 0.81-0.90, p=0.04] and a specialized surgeon in colorectal surgery [HR=0.85, 95% CI: 0.82-0.89, p=0.03] are two prognostic factors that improve the overall survival at 5 years, according to the meta-analysis of Archampong et al, which included 300 000 patients operated on for rectal cancer [28]. The high operating volume of hospital is also a prognostic factor [HR=0.90, 95% CI: 0.85-0.96, p=0.02] [28]. The surgeon's operating volume and the hospital operating volume have also been classified as prognostic factors in two studies of another meta-analysis that included 18 301 patients [HR=0.76, 95% CI: 0.63-0.90] [29].
A high operating volume and a specialized surgeon in colorectal surgery are two prognostic factors in rectal cancer with level I of evidence.

The approach
Since the advent of laparoscopy in 1991, its stand in terms of oncologic benefit still remains controversial [30-31]. Hang et al have shown, in a meta-analysis including 1033 patients, no statistical significant difference in terms of overall 3 years survival [HR=0.76, 95% CI: 0.54-1.07, p=0.11] and recurrence-free survival at 3 years [HR=1.16, 95% CI: 0.61-2.20, p=0.64] [32]. Ohtani et al have confirmed the results of the previous study through another meta-analysis that included 2095 patients, which concluded to the absence of statistically significant difference between laparoscopy and open surgery in terms of recurrence-free survival at 3 years s [OR=0.90, 95% CI: 0.66-1.24, p=0.62] and recurrence-free survival at 5 years [OR=1.17, 95% CI: 0.85-1.61, p=0.35] [33]. However, two other meta-analyses have concluded that laparoscopy reduced post-operative complications respectively [HR=0.71, 95% CI: 0.58-0.84, p=0.001][34] and [HR=0.83, 95% CI: 0.76-0.91, p<0.001] [35].
Wu et al have studied the place of endoscopic transanal resection in rectal cancers classified T1 [36]. They concluded that there was no statistically significant difference in terms of overall survival at 5 years between the endoscopic transanal way and the classical radical surgery (p=0.84) according to the results of a meta-analysis that included 397 patients [36].
The approach (laparoscopy or laparotomy) does not change the prognosis in rectal cancer with level I of evidence.
Ligation level of inferior mesenteric artery
The exact place of the ligation of the inferior mesenteric artery is not clearly defined: should it be tied as high as possible at its origin at the aorta? 1 cm after it arises from the aorta? or after the branch out of the left colic artery? A systematic review of literature published in 2013 concluded that high ligation of the inferior mesenteric artery did not improve overall 5 years survival [37]. However, overall 5 years survival was better with a higher ligation of the inferior mesenteric artery [OR=0.87, 95% CI: 0.76-0.98, p=0.02] according to the results of the meta-analysis of Chen et al [38].
The inferior mesenteric artery should be tied as high as possible to improve the prognosis and thus overall 5 years survival of rectal cancer: level II of evidence.

Total mesorectal excision
Overal survival was better after total mesorectal excision [OR=1.81, 95% CI: 1.55-2.11, p<0.00001] according to the meta-analysis of Liang et al which included 5267 rectal cancers [39].
Total mesorectal excision should be performed in rectal cancers to improve prognosis and overall survival: level I of evidence.

Abdominoperineal amputation (AAP)
There was no meta-analysis or systematic review of literature concerning abdominoperineal amputations for rectal cancers. Two prospective studies, of 2136 and 1219 patients respectively, compared abdominoperineal amputation and anterior resection in cancers of the lower part of the rectum [40-41].Overall survival at 5 years reached 55% for abdominoperineal amputation and at 68

% for anterior resection [40]. In the other study, overall survival at 5 years was 38,5% for abdominoperineal amputation and 57.6% for anterior resection [41].

Intersphincteric resection
Intersphincteric resection defined by Schiessel in 1994 is an attractive alternative that allows sphincter preservation in low rectal cancers [42]. Akagi et al, by means of a systematic literature review, have concluded that the median overall survival ranged between 79 to 97 months and the median recurrence-free survival between 69 and 86 months, without control group [43]. The authors concluded that despite the good results of the intersphincteric resection, a better knowledge in matters of surgical anatomy of pelvic nerves, of sphincter physiology is required to improve patients'survival [43].
In a prospective study that gathered 124 patients, Akagi et al compared overall survival at 5 years in the intersphincteric resection group and overall survival at 5 years in the abdominoperineal amputation group [44]. The authors concluded that there was no statistically significant difference in terms of overall survival at 5 years and thus for each stage of the tumour (stage I : 92.2% vs 87.5% p=0.32, stage II : 81.9% vs 67.3% p=0.37, stage III : 69.6% vs 62.1% p=0.37) [44].

Lymph node dissection
A lymph node dissection extending to the internal and external iliac chains did not improve either overall survival at 5 years [HR=1.09, 95% CI: 0.78-1.50, p=0.62] or recurrence-free survival [HR=1.23, 95% CI: 0.75-2.03, p=0.41] according to the meta-analysis of Georgiou et al which included 5502 patients [45]. These results have been confirmed by the meta-analysis of Cheng et al which included five studies [46].
A lymph node dissection extended to the internal and external iliac chains should not be performed in rectal cancer because it does not improve overall 5 years survival with level I of evidence.

3) Post-operative prognostic factors

Anastomotic leak
Overall survival at 5 years was significantly reduced in the group with leakage [66.4%, 95% CI: 60-72.7%] versus the no-leakage group [74.4%, 95% CI: 72.4-76.6%] with a Hazard ratio of 1.48, 95% CI: 1.19-1.83 (p<0.0001) according to the meta-analysis of Den Dulk et al which included 2726 patients [47].
Anastomotic leak worsens the prognosis of rectal cancer with level I of evidence.

Margin of surgical resection
Patients with R0 resection had a median overall survival extended by 37.6 months (95% CI: 23.5-51.7 months), compared to R1 resection group [HR=2.03, 95% CI: 1.73-2.38), and extended by a median of 53.0 months (95% CI: 31.2-74.8 months) compared to R2 resection group [HR=3.41, 95% CI: 2.21-5.25) according to the results of the meta-analysis of Bhangu et al which included 1460 patients [48].
Margin of surgical resection must be RO to improve prognosis in rectal cancer with level I of evidence.

Primary resection of rectal cancer
Survival at 5 years of non-operated stage IV rectal cancers is about 10 % [49]. Does the resection of stage IV rectal cancers have an influence on survival? In a retrospective study of 158 patients, the median survival was at 19.9 months in the resected group versus 19.0 months in the non-resected group [HR=0.81, 95% CI: 0.53-1.19, p=0.29] [50].The authors concluded that the resection of an asymptomatic stage IV cancer has no effect on survival [50].
Asymptomatic stage IV rectal cancers should not be resected because the resection does not improve survival with level III of evidence.

Adjuvant chemotherapy
Adjuvant chemotherapy improved overall survival [HR=0.83, 95% CI: 0.76-0.91, p<0.00001] and recurrence-free survival [HR=0.75, 95% CI: 0.68-0.83, p=0.03] after curative resection of rectal cancer, according to a systematic review of literature [51]. However, the authors concluded that the collected data do not allow them to assess the efficiency of chemotherapy based on the TNM stage [51].
Adjuvant chemotherapy ameliorates prognosis in rectal cancer with level I of evidence.

Time limit of adjuvant chemotherapy
Giving adjuvant chemotherapy beyond the 8th post-operative week was associated with worse overall survival in a meta-analysis which included 6677 resected rectal cancers [52].
Adjuvant chemotherapy should be given within no more than 8 weeks following the curative-aimed operation: level I of evidence.

Other post-operative prognostic factors
Other prognostic factors have been reported in literature, but with an insufficient level of evidence. We quote, without being exhaustive, the pathological factors and notably the vegetating macroscopic aspect which has a better prognosis, the tumor size higher than 5 cm , parietal invasion, node invasion and node ratio [53-55].

DISCUSSION

This systematic review allowed us to conclude that:
A high operating volume, a specialized surgeon in colorectal surgery, a partial response to neoadjuvant radiochemotherapy, a total mesorectal excision, an

adjuvant chemotherapy given within no more than 8 weeks following the curative resection improve prognosis in rectal cancer with level I of evidence.
Targeted therapy added to first-line chemotherapy improves prognosis in metastatic rectal cancer with level I of evidence.
Obesity and the approach (laparoscopy or laparotomy) do not change the prognosis in rectal cancer with level I of evidence.
Neoadjuvant radiochemotherapy does not improve the overall survival and reduces the risk of local recurrence in rectal cancer with level I of evidence.
A lymph node dissection extended to the internal and external iliac chains should not be performed in rectal cancer because it does not improve prognosis with level I of evidence.
Anastomotic leak and diabetes worsen prognosis in rectal cancer with level I of evidence.
Margin of surgical resection must be RO to improve prognosis in rectal cancer with level I of evidence.
The inferior mesenteric artery should be tied as high as possible and curative surgery must occur at least 8 weeks after the end of pre-operative radiochemotherapy in rectal cancer to improve the prognosis with level II of evidence.
CEA is an independent prognostic factor when its rate is higher than 5ng/ml in rectal cancer with level II of evidence. The complete response after adjuvant radiochemotherapy improve diagnosis in rectal cancer with level II of evidence.
Asymptomatic stage IV rectal cancers should not be resected because the resection does not improve survival with level III of evidence.

The main prognostic factors found in literature on which surgeons can act are reported in table 3.
After carrying out a literature review, we found only three articles that made the same work [56-58]. One article, in german, concluded that a distal resection margin of 2cm, total mesorectal excision, en-bloc resection of adherent structures, colonic pouch reconstruction after very deep resection and limitation of local excision to T1 grade 1 tumors were significant prognostic factors of rectal cancers and have to be regarded as standards of the surgical strategies [56].
The other article is in chinese, and there was not even an abstract, neither in english nor in another language [57]. A systematic review concluded that the only independent prognostic factor was total mesorectal excision, which improves overall survival and reduces local recurrence [58].

CONCLUSION

The main prognostic factors found in literature which we should keep in mind are those on which surgeons can act: neoadjuvant treatment, high operating volume of the surgeon, high tie of the inferior mesenteric artery, mesorectal excision , RO resection, improvement of the techniques of intersphincteric resection and techniques of anastomosis (low colorectal or coloanal) and adjuvant chemotherapy within less than 8 weeks when appropriate.

Table 3 : Prognostic factors in rectal cancer

Level of evidence	Pre-operative factors	Intra-operative factors	Post-operative factors
Level I	Diabetes	High operating volume of surgeon	Anastomotic leak
	neoadjuvant radiochemotherapy	surgeon specialized in colorectal surgery	margin of surgical resection
	targeted theray	total mesorectal excisim	Adjuvant chemotherapy
			Adjuvant chemotherapy ≤ 8 weeks
Level II	Carcinoembryonic antigen	Ligation level of inferior mesenteric artery	
	complete response after radiochemotherapy		
	curative surgery ≥ 8 weeks after radiochemotherapy		

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