Journal of Coloproctology

www.jcol.org.br

Original Article

Rectal cancer and chemoradiation in Iraq: systematic review and meta-analysis

Ahmed Salih Alshewered [a,*], *Manwar abdulelah Al-Naqqash* [b]

[a] *Misan Radiation Oncology Center, Misan Health Directorate, Ministry of Health/Environment, Misan, Iraq*
[b] *Department of Surgery, University of Baghdad, College of Medicine/Baghdad Radiotherapy and Nuclear Medicine Center/Oncology Teaching Hospital/National Cancer Center, Baghdad Medical City, Baghdad, Iraq*

ARTICLE INFO

Article history:
Received 29 May 2019
Accepted 17 June 2019
Available online 07 September 2019

Keywords:
Rectal cancer
Chemoradiation
Rectosigmoid
TMR
APR

ABSTRACT

Background: Rectal cancer is one of the most common malignant tumors of gastrointestinal tract. Combining chemotherapy with radiotherapy has a sound effect on its management.
Objectives: Assessment the patterns of characterizations of rectal cancer. Evaluation of the efficacy, and long-term survival of pre-/ postoperative chemoradiation. Collecting all eligible evidence articles and summarize the results.
Methods: By this systematic review and meta-analysis study, we include data of chemoradiation of rectal cancer articles from 2015 until 2019. The research was carried out at Baghdad Medical City oncology centers. Accordance with the PRISMA guidelines, and the Newcastle–Ottawa Scale used.
Results: Starting with gender distribution as M:F ratio of 0.94:1.06. Regarding the age, recorded mean ± SD of 48.7 ± 14.2 years. Rectosigmoid represented the most common site as 50(49.5%), and adenocarcinoma was common histopathology as 76(75.2%) of patients, with localized stage in 50(49.5%). The moderate differentiation was most grade as 65(64.4%). The distant from anal verge mostly seen was 5–10 cm in 59(58.4%). The pulmonary was commonest site of metastasis in 11(10.9%). Most patients undergo APR operation, which has done in 41(40.6%). Adjuvant chemoradiation received by 40(39.6%) patients, whereas neoadjuvant chemoradiation gave to 25 patients. A total of 2609 articles from 12 databases met our search strategies. The highest Newcastle–Ottawa score (8) demonstrated in three studies, and median score (7) calculated in five studies.
Conclusions: The incidence belonged to 5th and 6th decade of life. Rectosigmoid represented the most common site. Mostly, the 5–10 cm distant of tumor from anal verge was common finding. The pulmonary was most site of metastasis. We concluded the formulation of a novel point that survival benefit found in many pre or postoperative chemoradiation trials in rectal cancer.

* *Corresponding author.*
E-mail: ahmedsalihdr2008@yahoo.com (A.S. Alshewered).
https://doi.org/10.1016/j.jcol.2019.06.003

Câncer retal e quimiorradioterapia no Iraque: revisão sistemática e metanálise

Palavras-chave:
Câncer retal
Quimiorradioterapia
Retossigmoide
TMR
Ressecção abdominoperineal

RESUMO

Introdução: O câncer retal é um dos tumores malignos mais comuns do trato gastrointestinal. A combinação de quimioterapia e radioterapia em seu tratamento é eficaz.
Objetivos: Avaliar os padrões de caracterização do câncer retal. Avaliar a eficácia e sobrevida a longo prazo em pacientes submetidos a quimiorradioterapia pré- ou pós-operatória. Coletar todos os artigos de evidências qualificados e resumir os resultados.
Métodos: Esta revisão sistemática e metanálise incluiu dados de ensaios clínicos randomizados por *cluster* de 2015 até 2019. A pesquisa foi realizada nos centros de oncologia do Baghdad Medical City. As diretrizes PRISMA e a escala de Newcastle-Ottawa foram utilizadas para avaliar os estudos.
Resultados: Quanto à distribuição por sexo, observou-se uma relação homem:mulher de 0,94:1,06. Em relação à idade, a média ± DP foi de 48,7 ± 14,2 anos. O retossigmoide fpo o local mais comum em 50 pacientes (49,5%); a histopatologia mais comum foi adenocarcinoma, observada em 76 pacientes (75,2%), com estágio localizado em 50 (49,5%). Diferenciação moderada foi observada em 65 pacientes (64,4%). A distância da borda anal variou entre 5 e 10 cm em 59 pacientes (58,4%). O pulmão foi o local mais comum de metástase, sendo observado em 11 pacientes (10,9%). A maioria dos pacientes (41 [40,6%]) foi submetida à ressecção abdominoperineal. Um total de 40 pacientes (39,6%) foram submetidos a quimiorradioterapia adjuvante e 25, a quimiorradioterapia neoadjuvante. Na revisão da literatura, foram encontrados 2.609 artigos que atendiam aos critérios de pesquisa utilizados em 12 bancos de dados. Três estudos atingiram o escore máximo na escala de Newcastle-Ottawa (8); cinco estudos atingiram o escore mediano (7).
Conclusões: No presente estudo, a maior incidência de câncer retal foi observada entre a quinta e sexta décadas de vida. O retossigmoide foi o sítio tumoral mais comum. A maioria dos tumores estava localizado entre 5 a 10 cm de distância da margem anal. O pulmão foi o local mais importante de metástase. No presente estudo, quimiorradioterapia pré- ou pós-operatória estava relacionada a uma maior sobrevida em casos de câncer retal.

Introduction

In 2011, recorded 1086 cases of colorectal cancer by the Iraqi Cancer Registry (ICR), as 5.3% of most ten cancer types in Iraq, whereas in 2015 the ICR recorded 1454 patients as 5.7%.[1,2] Globally the new cases are diagnosed at 2018 worldwide, accounting 704,376 (3.9%) of human cancers.[3] The primary therapy for potentially curative rectal cancer is surgery.[4] Curative surgery should excise the tumor with wide margins and maximize regional lymphadenectomy such that at least 12–15 lymph nodes are available for pathologic evaluation.[5] While the current standard therapy for stage III rectal cancer, and sometimes for stage II disease, is preoperative chemotherapy using 5-FU and RT, followed by surgery, and then followed by adjuvant chemotherapy.[6] Because of the anatomic confines of the pelvic bones and sacrum, surgeons often cannot achieve wide, tumor-free margins during the resection of rectal cancer. Patients who have a complete pathologic response to preoperative therapy have a favorable long-term prognosis.[7] The most commonly used chemotherapeutic agents are 5-FU, capecitabine, irinotecan, and oxaliplatin.[7] For those with advanced stages, all regimens can be used, whereas in metastatic setting addition of Bevacizumab or Panitumumab or Cetuximab can be of benefit.[7] CRT (RT + 5FU or capecitabine) can be used preoperatively or postoperatively.[6] GITSG 7175 trial deal with stage B2-C rectal cancer randomized postoperatively to no adjuvant therapy vs. chemo alone vs. RT alone vs. concurrent CRT. CRT arm improved 5-year DFS and OS over control.[7] The NSABP R-01, R-02 trials reported rectal cancer with B-C (II–III) treated with surgery alone vs. post-op RT vs. post-op chemo. RT improved LF (25 vs 16%), while chemo improved DFS (30 vs 42%) and OS (43 vs 53%) vs. observation. The EORTC trial 22921 trial found a significant decrease in the local failure rate in those patients who receive chemoradiation compared with irradiation (8–10% versus 17%; $p < 0.001$) but no difference in the 5-year OS (65%).[8] The NSABP R0-354 and the German CAO/ ARO/AIO 94 trials suggesting that chemotherapy increased the response rate of preoperative radiation.[9] Short-course radiation (25 Gy in 5 fractions) was established as a standard therapy in the Dutch Colorectal Cancer Group CKVO and Swedish Rectal Cancer trials and CRT was created as a standard therapy by the German Rectal Cancer Trial CAO/ARO/ AIO-94 (45–50.4 Gy in 25–28 fractions plus concurrent chemotherapy).[10,11] Polish Colorectal Study Group trial showed a higher pCR rate

(16% versus 1%) and a lower incidence of positive radial margins (4% versus 13%, p = 0.017).[12] Pooled-analysis on NCCTG trials, Int 0144, NSABP RO1, and RO2, revealed that post-op chemo appeared to improve OS, similar to post-op chemoradiation, but DFS, OS, and LF tended to be better with chemoradiation.[13]

Methods

Study setting

In this systematic review and meta-analysis study, we included data of chemoradiation roles in the management of rectal cancer, with time limitations from 2015 until 2019. Finally, through 2609 related articles reviewing and searching, nine articles were included. The research process was carried out in three centers at Baghdad Medical City including: Baghdad Radiotherapy and Nuclear Medicine Center, Oncology Teaching Hospital, and National Cancer Center.

Study design

Under accordance with the PRISMA guidelines,[14] and measured the quality of the studies based on the Newcastle–Ottawa Scale.[15] The scale assessed the selection of studies, and ascertainment of each one. Each positive criterion scores 1 point, with the maximum N–O score is 9.

Inclusion criteria

1 All English-language articles related to chemoradiation management of rectal cancer.
2 All methods of study, and thesis that associated with the subject of this research.
3 All trials that compare pre-/post-operative chemoradiotherapy.
4 Cross–sectional or observational studies with >50 patients.

Exclusion criteria

1 The non-English-language articles, as were those without full-text access.
2 Scientific documents related to predatory origin.
3 All duplicate articles and records.
4 All literature that the patients presented with colon cancer or anal cancer only.
5 The study was a randomized controlled trial.

Data sources

The international electronic databases investigated and including English sources from Medline through PubMed, Google Scholar, ResearcGate, Scopus, Embase, ISI Web of Science, Springer databases, ScienceDirect, and the Cochrane Library, were searched and selected. Iraqi Academic Scientific Journals, The Eastern Mediterranean Journals, and African Journals OnLine were also searched for published articles, and other documents were extracted from reports published by organizations.

Data extraction and collection

The primary data reported included rectal cancer, and patients study characterizes of 101 patients attending Oncology centers. Those, including the gender, age, family history, smoking, comorbidity, IBD, tumor sites, histopathology, stages, grading, distance for anal verge, local recurrence, distant metastasis, type of surgery, CRT details of neoadjuvant and adjuvant therapy. Others for systematic and meta-analysis studies data included time, country, study type, the patients number, treatment types, and year of publication.

Search strategy

The search for articles was done using a combination of groups of words in the databases mentioned above: rectum (rectal cancer OR rectum tumor OR rectal neoplasm), chemoradiation (chemotherapy OR radiotherapy OR pre-operative OR post-operative OR neoadjuvant OR adjuvant OR chemoradiation OR chemoirradiation OR radio-chemotherapy), surgery (anterior resection of rectum OR total mesorectal excision OR abdominoperineal resection OR anterior resection of rectum), and study (systematic review OR meta-analysis OR cross-sectional OR observational), and (chemoirradiation trials). These groups of words were combined with “AND” together, and used in titles, abstracts, and keywords of used articles.

Statistical analysis

All data collected were entered into excel sheet folder, transferred then for statistical analysis into a file of Statistical Package for Social Sciences version 24 (SPSS v24) (SPSS Inc., Chicago, Illinois, USA). Descriptive analysis of clinical and pathological characteristics was performed. Performed PRISMA flowchart for inclusion and exclusion studies. Assessed the N–O score for including studies with several confounding variables we collected. Forset plot used to showed comparison between neoadjuvant and adjuvant CRT roles in rectal cancer. A non-random-effects model used for meta-analysis of all studies by Odds ratios at 95% CI.

Results

Patients baseline characterizers

Gender distributed as male 49(48.5%), and female 52(51.5%). Regarding the age groups, we recorded 25(24.8%) of patients belonged to 61–70 years, and 20(19.8%), 24(23.8%), 6(5.9%) of them for 41–50 years, 51–60 years, 21–30 years, respectively, with mean ± SD = 48.7 ± 14.2 years. Of all 101 patients, there was only 7(6.9%) had a positive family history. Smoker patients in this study were 50(49.5%), yet the non-smoker patients were 51(50.5%). The comorbid conditions company rectal cancer found in 46(45.5%). The IBD were presented in 5(4.9%) patients, whereas the majority were absent as 96(95.1%), as shown in (Table 1).

Table 1 – Patients baseline characterizers of rectal cancer (n = 101).

Characterizes		n (%)
Gender	Male	49 (48.5)
	Female	52 (51.5)
Age (years) Mean ± SD = 48.7 ± 14.2	<20	0
	21–30	6 (5.9)
	31–40	13 (12.9)
	41–50	20 (19.8)
	51–60	24 (23.8)
	61–70	25 (24.8)
	>70	13 (12.9)
Family history	Positive	7 (6.9)
	Negative	94 (93.1)
Smoking	Smoker	50 (49.5)
	Non-smoker	51 (50.5)
Comorbidity	Present	46 (45.5)
	Absent	55 (54.5)
IBD	Present	5 (4.9)
	Absent	96 (95.1)

Table 2 – Tumor baseline characteristics of rectal cancer (n = 101).

Characteristic		n (%)
Location	Rectosigmoid	50 (49.5)
	Rectum	42 (41.6)
	Anorectal	9 (8.9)
Histopathology	Adenocarcinoma	76 (75.2)
	Mucinous carcinoma	13 (12.9)
	Signet-ring cell carcinoma	4 (4)
	Undifferentiated carcinoma	7 (6.9)
	Adenosequomous carcinoma	1(1)
Stages	Localized	50 (49.5)
	Regional	19 (18.8)
	Distant metastasis	32 (31.7)
Grades	Well differentiation	20 (19.8)
	Moderate differentiation	65 (64.4)
	Poorly differentiation	14 (13.9)
	Undifferentiation	2 (2)
Distant from anal verge	<5 cm	13 (12.9)
	5–10 cm	59 (58.4)
	>10 cm	29 (28.7)

Tumor baseline characterizers

Rectosigmoid cancer represented the most common site in this study as 50(49.5%), while rectum, and anorectal were presented as 42(41.6%), and 9(8.9%), respectively. The results showed prominent of adenocarcinoma as most common histopathology as 76(75.2%) of patients. The localized stage of cancer recorded in 50(49.5%) patients. Regarding cancer grading, the moderate differentiation was dominant grade as 65(64.4%). The tumor distant from anal verge results exhibited as <5 cm in 13(12.9%), 5–10 cm in 59(58.4%), and >10 cm in 29(28.7%), as shown in (Table 2).

Metastasis pattern of rectal cancer

The majority of patients of our study have no metastatic disease as 68(67.3%). Indeed the pulmonary was the most frequent site of distant metastasis that found in 11(10.9%) patients, as well as multiple organs metastasis presented in 10(9.9%) patient. Furthermore, local recurrence found in 7(6.9%) patients, whereas liver and bone secondaries showed the lowest site of metastasis as 2(2%), 3(3%), respectively, as shown in (Table 3).

Table 3 – Rectal cancer metastasis patterns (n = 101).

Characteristic		n (%)
Metastatic patterns	Liver	2 (2)
	Lung	11 (10.9)
	Local recurrence	7 (6.9)
	Bone	3 (3)
	Multiple metastases	10 (9.9)
	No metastases	68 (67.3)

Table 4 – Rectal cancer management (n = 101).

Variables		n (%)
Surgery	APR	41 (40.6)
	LAR + loop ieliostomy	4 (4)
	LAR without ieliostomy	3 (3)
	TME	23 (22.8)
	Local excision	5 (5)
	No surgery	25 (24.8)
Chemoradiation	Neoadjuvant chemotherapy + CRT	12 (11.9)
	Neoadjuvant RT + Adjuvant chemotherapy	4 (4)
	Neoadjuvant CRT	7 (6.9)
	Neoadjuvant CRT + Adjuvant chemotherapy	6 (5.9)
	Adjuvant CRT	40 (39.6)
	Palliative CRT	32 (31.7)

Rectal cancer treatment

APR and TME were the prevalent two operations have done in 41(40.6%), 23(22.8%), respectively. Whatever those who have no surgery done for them at all were 25(24.8%). CRT used in most of the management programs. Adjuvant CRT performed in 40(39.6%), whereas neoadjuvant CRT was given for 25 patients as neoadjuvant chemotherapy + CRT 12(11.9%), neoadjuvant chemotherapy only 7(6%), and neoadjuvant CRT + adjuvant chemotherapy 6(5.9%). Radiotherapy or chemotherapy as alone method for treatment, recorded in 4(4%) of patients. Lastly, palliation modalities were used in 32(31.7%) of patients, as shown in (Table 4).

Meta-analysis findings

A total of 2609 articles with 1377 citations from 12 databases met our search strategies about rectal cancer were searched from 2015 to 2019. Duplication screening done resulted in 789 articles were excluded after reviewing of titles/abstracts. Then 132 articles retrieved after the second review. In the full articles text screen a total of 356 article were excluded. Also, during the process of data extraction, 91 articles were excluded. Finally, Nine studies were included in a meta-analysis of our study after reviewing of the full-text articles that adequately match the inclusion and exclusion criteria, as shown in (Fig. 1) (All references listed in the supplementary file are for the nine studies included). The highest Newcastle–Ottawa score (8)

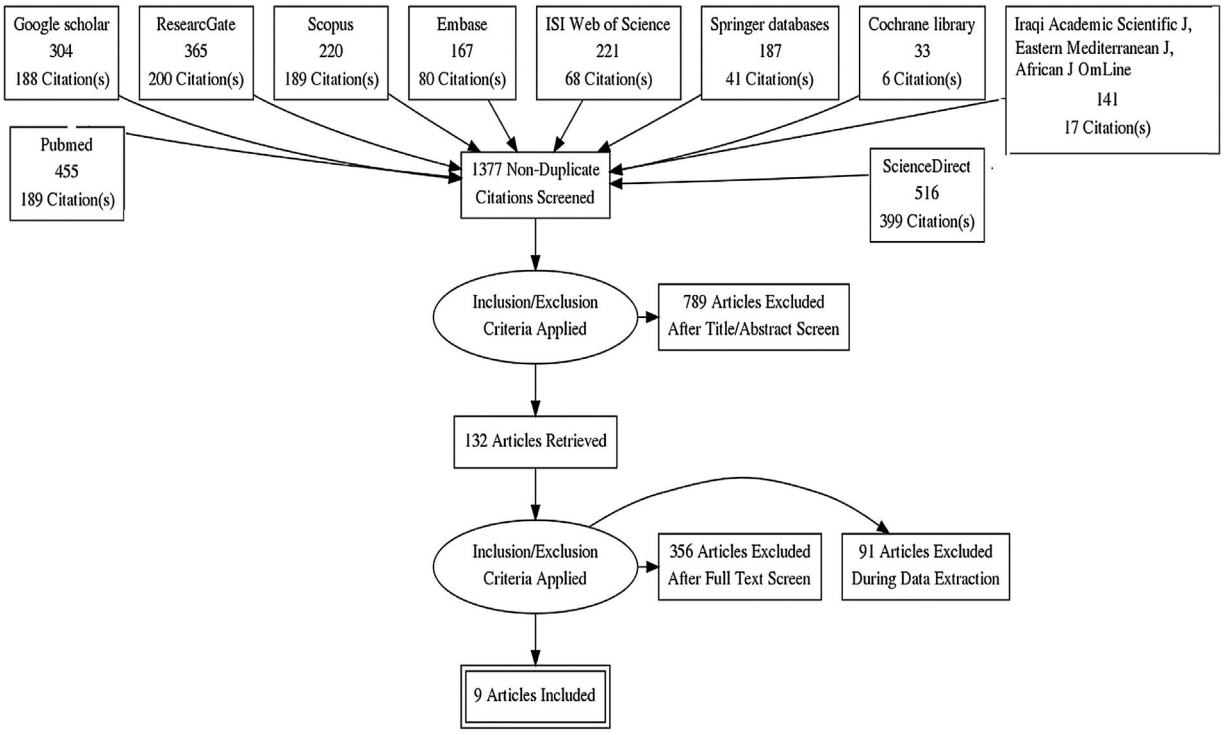

Fig. 1 – PRISMA flowchart to include and exclude articles of chemoradiation roles in the management of rectal cancer in this study.

demonstrated in three studies, which were Ellis 2019; Spiegel 2018; Mancini 2017, whereas median score (7) calculated in five studies, they were Chapman 2019; Quezada-Diaz 2019; Franke 2017; Dossa 2017; Rodel 2016. Lastly, the low score (6) obtained in Kimberly 2017 only, as showed in (Table 5). All nine articles described chemoradiation as the main subject in the management of rectal cancer. Three articles conducted in 2019 by Ellis CT; Chapman W; Quezada-Diaz F, one in 2018 by Spiegel D, four in 2017 by Mancini R; Franke AJ; Dossa F; Kimberly P, and one in 2016 by Rodel C, as shown in (Table 6). Different study models used, different sample size, and period. Comparison, cohort, systematic review, analysis, meta-analysis, and randomized studies were thoroughly reviewed in details. Many outcomes obtained range from the complete response, improvement in OS, DFS, and LR. Most of the patients in nine studies undergo TMR as the main surgical operation (Table 6). Forset plot showed comparison between two arms of CRT with overall shifted to neoadjuvant side at heterogeneity was $I2 = 73.1$; $P = 0.001$. A non-random-effects model was used with all studies Odds ratios at 95%CI (Fig. 2).

Discussion

Our findings regarding gender estimated 49(48.5%) were men, and 52(51.5%) were women. Similarly, results were reported by Radhi et al., 2018 in Al-Diwaniyah,[16] Alsafi et al., 2018 in Karbala,[17] whereas different from studies conducted in Misan by Alhilfi et al., 2019,[18] and Khalil et al., 2018 in Duhok.[19] A report registered in the Iraqi cancer registry for the period 2002–2011 and in the National Cancer Hospitals between 2012 and 2014, found that male to female ratio varied from 1.17:1 to 1.28:1.[20] Belong to the age groups, the peak incidences were found in 25(24.8%) of patients to 61–70 years, and 24(23.8%) of patients to 51–60 years. These findings, like many data reported by studies in our country and worldwide status.[15–23] Of all 101 patients, there was only 7(6.9%) had a positive family history. Tobacco smoking as a risk factor presented in 50(49.5%) of patients. The comorbid conditions company rectal cancer found in 46(45.5%). Furthermore, the IBD was presented in 5(4.9%) patients only. Many factors shown to increase the risk of developing colorectal cancer including: increasing age; male sex; family history; inflammatory bowel disease; increasing height; increasing body mass index; consumption of processed meat, refined grains, starches, and sugars; excessive alcohol intake and smoking; and low folate consumption.[7] Of these, only increasing age, male sex, and excessive alcohol use have been associated with rectal cancer.[21]

The tumor characteristics revealed that rectosigmoid cancer represented the most current site as 50(49.5%) of patients. This information resembling many studies outside Iraq,[22,23] whereas disagreeing with Radhi et al., 2018,[16] Alsafi et al., 2018,[17] Alhilfi et al., 2019,[18] and Khalil et al., 2018[19] studies. Those may be estimated the non-real figures because of many patients prefer to do a colonoscopy in the different provinces and even outside the country, besides that many cases of rectal cancer diagnosed by imaging studies such as CT scan or the US and undergo surgery without doing colonoscopy or sigmoidoscopy.

On the other hand, we received many cases for colonoscopy referred to the center from other provinces so that figures may not reflect the distribution of the disease site or locations. The highest recto-sigmoid cancer incidence rates are found in Europe (eg, Hungary, Slovenia, Slovakia, the Netherlands,

Table 5 – Newcastle–Ottawa scale of the eligible nine studies.

Newcastle–Ottawa scale										
Study ID	Is the definition adequate?	Is it representative?	Selection adequate	Definition of meta-analysis adequate	Study for the most important factor	Study for Important Additional factors	Ascertainment adequate	Same method of ascertainment	Non-response rate adequate	Total score /9
Ellis 2019	yes	yes	yes	yes	yes	yes	unclear	yes	yes	8
Chapman 2019	yes	yes	unclear	yes	yes	yes	yes	unclear	yes	7
Quezada-Diaz 2019	yes	yes	unclear	yes	yes	yes	yes	yes	no	7
Spiegel 2018	yes	yes	yes	yes	yes	no	yes	yes	yes	8
Mancini 2017	yes	yes	yes	no	yes	yes	yes	yes	yes	8
Franke 2017	yes	yes	yes	no	yes	yes	yes	yes	unclear	7
Dossa 2017	yes	yes	yes	yes	yes	yes	unclear	yes	unclear	7
Kimberly 2017	yes	yes	yes	no	no	yes	yes	yes	unclear	6
Rodel 2016	yes	yes	yes	yes	yes	yes	unclear	yes	unclear	7

Table 6 – Meta-analysis of the eligible nine studies.

Study	Type	*n* of patients	Chemoradiation	Follow up period	Outcome	Conclusions	N–O score
Ellis et al., 2019[1]	Comparison SEER-Medicare	482	Adjuvant/neoadjuvant plus surgery	24 month	2.5%/3.4% complete response	Treated with CRT-only were less likely to receive surveillance than those treated with conventional treatment	8
Chapman et al., 2019[2]	Retrospective cohort study	388	Neoadjuvant, and TMR	9 years	pCR rate of 25% and overall recurrence rate of 14.9%	Short course radiation with neoadjuvant multi-agent chemotherapy is at least as effective as long-course CRT	7
Quezada-Diaz et al., 2019[3]	Retrospective review	176	Adjuvant, neoadjuvant, and surgery	6 years	–	The trimodality treatment does not seem to impair bowel function	7
Spiegel et al., 2018[4]	Veterans Health Administration analysis	649	Adjuvant, neoadjuvant, and TMR	66 months	Improve both OS and DFS	There was no improvement in OS or DFS with the addition of a multi-agent over single-agent chemotherapy	8
Mancini et al., 2017[5]	Multiple correspondence analysis	174	Neoadjuvant plus surgery	10 years	13.2% complete response	Neoadjuvant CRT and radical surgery enrich the prognostic profile of patients	8
Franke et al., 2017[6]	Systematic review	–	Neoadjuvant plus surgery	5 years	Reduced local recurrence rates	Outline the pragmatic opportunities for future investigation into questions of efficacy, safety, and ultimate improvements	7
Dossa et al., 2017[7]	Systematic review and meta-analysis	867	Neoadjuvant plus watch-and-wait	12–68 months	–	Most patients treated by watch-and-wait avoid radical surgery and of those who have regrowth almost all have salvage therapy	7
Kimberly et al., 2017[8]	Phase II randomized trial	93	Adjuvant and neoadjuvant plus surgery	4 years	All patients had resolution of bleeding and improvement of obstructive symptoms, with no complications requiring surgical intervention.	TRIAL seems to be a well-tolerated alternative to the current standard treatment sequence.	6
Rodel et al., 2016[9]	Meta-analysis	–	Preoperative/postoperative plus TMR		Encouraging pCR rates but increased surgical complications	The benefit role of induction and consolidation chemotherapy before or after CRT. The minimal or omitted surgery following complete response to CRT The omission of radiotherapy for selected patients with response to neoadjuvant chemotherapy.	7

CRT, chemoradiation; pCR, pathological complete response; OS, overall survival; DFS, disease free survival; TMR, total mesorectal resection; N–O, Newcastle–Ottawa.

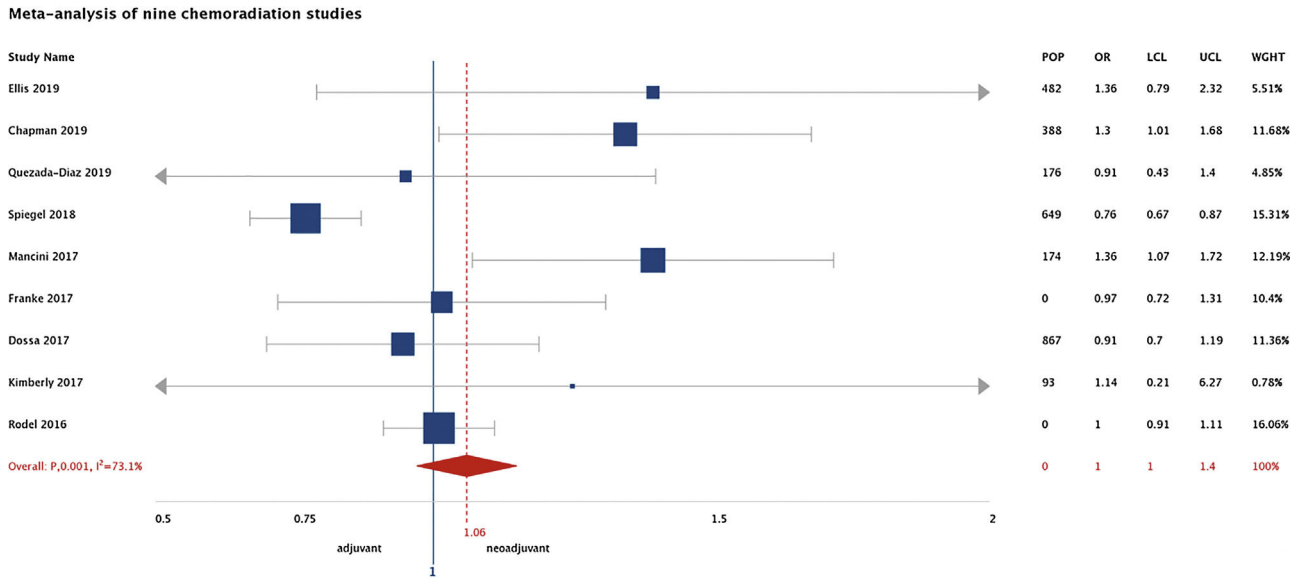

Fig. 2 – Forest plot showing chemoradiation roles in rectum cancer. A non-random-effects model was used for meta-analysis. Odds ratios are shown with 95%CI.

and Norway), Australia/New Zealand, Northern America, and Eastern Asia (Japan and the Republic of Korea, Singapore [in females]), with Hungary and Norway, rates also are elevated in Uruguay among both men and women. Rectal cancer incidence rates have a similar regional distribution, although the highest rates are seen in the Republic of Korea among males and Macedonia among females. Rates of both colon and rectal cancer incidence tend to be low in most regions of Africa and Southern Asia.[3,7]

The results showed prominent of adenocarcinoma as most common histopathology as 76(75.2%) of patients, with localized stage of cancer recorded in 50(49.5%) patients, and the moderate differentiation was dominant grade as 65(64.4%). Tumors of the rectum arise in the mucosa, and virtually all (>90%) are adenocarcinomas.[21] Most grading systems classify adenocarcinoma as well, moderately or poorly differentiated.[21] All studies conducted in various provinces in our countries demonstrated the same results.[15–20, 24] Mostly, the 5–10 cm distant of tumor from the anal verge was the common finding exhibited as 59(58.4%) of patients. Khan et al., concluded that the distance of rectal cancer from the anal verge influenced the use of neoadjuvant treatment and ultimate R0 resection rate.[25] The tumor location and the distal tumor margin are essential factors upon which the surgical plan for patients with rectal cancer is based. Accurate measurement of the distal tumor margin is necessary in planning the surgical procedure, sphincter-saving resection.[25]

The pulmonary site was most frequent site of distant metastasis that found in 11(10.9%) patients, as well as multiple organs metastasis presented in 10(9.9%) patient. Large-bowel tumors invading from mucosa through the wall and beyond that, with the involvement of lymphatic vessels and lymph nodes, as well as the hematogenous spread can occur, primarily to the lung and liver.[21] Pulmonary metastasis occurred more frequently in patients with lower rectal cancer than in those with upper rectal cancer.[7,21] Rectal cancers are three times more likely to recur locally than are proximal colonic tumors, because the anatomic confine of the rectum precludes wide resection margins, and the rectum lacks an outer serosal layer through most of its course. Due to the venous and lymphatic drainage of the rectum go to the inferior vena cava, it has a higher incidence of lung metastasis compared with colon cancers that more frequently recurs first in the liver.[7,21]

Information regarding types of surgery were inadrquate in our country due to inadequate surgical reports written. Many procedures perform for radical surgery of rectal cancer like Hartmann procedure, total proto- coloctomy, anterior resection, APR, and ileal pouch- anastomosis. Most patients of our study undergo APR and TME operations, were the most prevalent two procedures have done in 41(40.6%), 23(22.8%), respectively. CRT used in most of management modalities. Adjuvant CRT performed in 40(39.6%), whereas neoadjuvant CRT was given for 25 patients as neoadjuvant chemotherapy + CRT 12(11.9%), neoadjuvant chemotherapy only 7(6%), and neoadjuvant CRT + adjuvant chemotherapy 6(5.9%). Radiotherapy or chemotherapy as alone method for treatment, recorded in 4(4%) of patients. Lastly, palliation modalities were used in 32(31.7%) of patients. Most trails and studies conducting to demonstrating good outcomes of chemoradiation in rectal cancer have a significant improvement in survival and patient quality life. The National Cancer Institute (NCI) and Mayo/NCCTG 79-47-51 trials; NSABP R-01, R-02 trials; EORTC trial 22921; NSABP R0-354 and the German CAO/ ARO/AIO 94 trials; STAR-01, ACCORD, and NSABP R-04 trials; UK MRC CR07 trial; Dutch Colorectal Cancer Group CKVO, and Swedish Rectal Cancer trials; German Rectal Cancer Trial CAO/ARO/ AIO-94; Polish Colorectal Study Group trial, all improved the DFS, OS, and LF tended to be better with chemoradiation.[7–13]

The present meta-analysis demonstrates a significant reduction in local recurrence rate with the addition of chemotherapy over all nine studies. Importantly, the

summation of incidence rates of local recurrence of radiotherapy group of the nine studies were 17%, and in both groups were 15%, that seem it is a high compared to the 5.5% local recurrence rate at 5 years achieved by the Dutch rectal cancer trial use pre-operative RT followed by surgery [11,14]. Differences in stage distribution and variation in surgical technique might be the cause. Indeed, during the Dutch rectal cancer trial, a formal surgical training and quality control program was implemented to guarantee optimal surgery TME.[6] Although in the studies of 2017 by Mancini et al.; Franke et al.; Dossa et al.; Kimberly et al., a marginally significant five year survival benefit were associated with CRT, the combined analysis resulted in demonstrating a significant difference in either OS or DFS.

This formulated as a novel point of our study to explain that survival benefit found in many pre or postoperative adjuvant therapy trials in rectal cancer. But, we have argued that the follow-up time of our study is too short to observe a survival benefit. The results of this meta-analysis confirm the enhanced antitumor efficacy of combined RT with chemotherapy. Also showed that compared to preoperative RT alone, preoperative CRT improves local control in resectable rectal cancer. Those represent the novel findings of our study, which are primarily described as the first study done in Iraq, other novelty that the description of a significant association between most of the tumor characters and management multimodalities. The role of preoperative CRT before radical surgery is to delay the development of pelvic recurrence of tumor, in the other words, it to decrease the failure rate. Also, it might cause down- staging or down- sizing of the tumor, that lead to feasible for getting close circumferential resection margin, which might resulted enhance the effectiveness in well oxygenation of tissue for more repair. Beside to save anal sphincter preservation. Addition of chemotherapy agents to RT is for act as radiosensitizer to enhance RT effect on the primary tumor, this might cause complete sterilized of tumor after complete surgical resection. But here may be still there are micro- metatatic cells not die.

Conclusions

The incidence of rectal cancer is mostly belongs to 5th, and 6th decade of life. The family history, tobacco smoking, comorbid conditions, and the IBD behave unmarked effect as risk factors. Rectosigmoid cancer represents the most common site, follow by rectum, with prominent of adenocarcinoma as most common histopathology, and of moderate differentiation grade. Mostly, the 5–10 cm distant of tumor from anal verge was the common finding exhibited, and this importantly in influenced the use of neoadjuvant treatment and planning the surgical procedure. The pulmonary was most typical site of distant metastasis followed by multiple organs metastasis. All relation between cancer characters, surgical operations, and CRT demonstrated significant differences. We meta-analyzed a significant reduction in local recurrence rate with the addition of chemotherapy to radiotherapy. The formulated a novel point that survival benefit found in many pre or postoperative CRT trials in rectal cancer. Here all patients are electively selected as we deal with those who received CRT in our centers, but due to that a lot of patients may be the majority should be discovered, hence rectosigmoid tumor present as emergency conditions as intestinal obstructions, which may be hidden.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcol.2019.06.003.

REFERENCES

1. Iraqi Cancer Registry. Ministry Of Health, Iraqi Cancer Board, Baghdad, Iraq; 2011 https://moh.gov.iq/upload/upfile/ar/273.pdf
2. Iraqi Cancer Registry. Annual Report. Iraqi Cancer Registry Board, Ministry Of Health and Environment. Baghdad, Iraq; 2015.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin. 2018;68:394–424.
4. NCCN. Clinical Practice Guidelines in Oncology. Rectal Cancer Version.2; 2019 www.nccn.org.
5. Alberts SR, Grothy A. In: Casciato DA, Territo MC, editors. Manual of Clinical Oncology: Colorectal cancer. 7th ed. USA: Lippincott Williams & Wilkins, a Wolters Kluwer business; 2012. p. 239–58.
6. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol. 2007;25:4379–86.
7. Mohiuddin M, Willett CG, et al. In: Halperin EC, Perez CA, Brady LW, editors. Principles and practice of radiation oncology: Colon and Rectum, 2015, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2015. p. 1366–82.
8. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol. 2014;15:184–90.
9. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30:1926–33.
10. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG Co16 randomised clinical trial. Lancet. 2009;373:821–8.
11. Bosset JF, Collette L, Bardet E, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. New Engl J Med. 2006;355:1114–23.

12. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol. 2006;24:3542–7.
13. Gunderson LL, Sargent D, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol. 2004;22:1785–96.
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097.
15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Ottawa Hospital Research Institute; 2019 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
16. Radhi AA, Muslim OT, Abdlmaged MA. Epidemiological distribution of colorectal cancer in AL-Diwaniyah province, Iraq: an observational study. J Pharm Sci Res. 2018;10:1758–60.
17. ALSafi RAR, Metib NJ, Hameedi AD, et al. The clinical and pathological characteristics of colorectal cancer in young age group in Karbala Province/Iraq. Karbala J Med. 2018;11:4025–31.
18. Alhilfi HSQ, Almohammadawi KOM, Alsaad RKA, et al. Colorectal cancer epidemiology and clinical study in Misan. J Coloproctol (RIO J). 2019;9:159–62.
19. Khalil KH, Al-Hassawi BA, Abdo JM. Histopathological evaluation of colorectal carcinoma. Duhok Med J. 2018;12:45–68.
20. Al-Dahhan SA, Al-Lami FH. Epidemiology of colorectal cancer in Iraq, 2002-2014. Gulf J Oncolog. 2018;1:23–6.
21. Palta M, Willett CG, Czito BG, et al. In: Halperin EC, Perez CA, Brady LW, editors. Principles and practice of radiation oncology: Cancer of the Colon and Rectum. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 1215–30.
22. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
23. SEER. Surveillance, Epidemiology, and End Results. Stat Fact Sheets: Rectal Cancer. Archived from the original on 3 July 2014. Retrieved 18 June 2014. https://seer.cancer.gov.
24. Almohammadawi KOM, Alhilfi HSQ, Alshewered ASH. Epidemiological data of 1418 Cancer Cases of Inpatient in Al-Sadder Teaching Hospital, Misan Province from 2011–2018 (Surveillance Study). Med. Sci. 2018;22(93):455–61.
25. Khan MAS, Ang CW, Hakeem AR. The impact of tumour distance from the anal verge on clinical management and outcomes in patients having a curative resection for rectal cancer. J Gastrointest Surg. 2017;21:2056–65.