Archives of the Balkan Medical Union
vol. 51, no. 1, pp. 57-62
March 2016

REVIEW

THE RELATIONSHIP BETWEEN CHEMORADIOTHERAPY AND THE "SPHINCTER SAVING" RATE IN THE CURRENT TREATMENT OF RECTAL CANCER

Alina Cristina Tinca[1,2], R. Palade[2], D. Ion[1,2], R.V. Stoian[1,2], Alexandra Bolocan[1,2], Emel Suliman[2], M.B. Șerban[1,2], D.N. Păduraru[1,2]

[1]General Surgery and Emergency Clinic III, University Emergency Hospital Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Summary

Introduction: Rectal cancer is a major public health problem with severe implications in the economic and social sphere, the complex treatment, of which both surgical and medical, requires constant changes and improvements that have as major objective the preservation of the quality of life in optimal oncological conditions. In the complex oncological and surgical treatment of any type of cancer, organ preservation is a therapeutic success. For patients with rectal cancer located in a low position, it is obvious that anterior resection with preservation of the sphincter apparatus (SP), when feasible, results most often in better life quality and lower morbidity compared to secondary abdominal-perineal resection and it also does not compromise the oncological outcome.
Material and method: In order to accomplish this analysis specialty literature was revised and articles published between 2005 and 2015 and relevant to the topic under discussion were studied.
Results: There are studies that provide encouraging information on obtaining better SP rates, depending on the preoperative protocol of radiation used: short or long, with/without chemotherapy, with long / short post therapeutic period until surgery. The role of perioperative radiation therapy for the treatment of resectable rectal cancer is obvious in what conerns the decrease of local relapses, compared to the radical surgical resections with no radiation. Adding radiotherapy leads to a significant improvement in local control, reduced toxicity, but failed to reduce overall mortality and to also increase the number of resections with SP.
Conclusions: Rectal cancer treatment still requires a multidisciplinary management that constantly adapts the multitude of therapeutic strategies to each case in particular. The neoadjuvant therapy is an indispensable part in the treatment algorithm and improved oncologic outcome should be the primary objective.

Résumé

La relation entre la chmio-radio-thérapie et le taux de préservation du sphincter dans le traitement courant du cancer rectal

Introduction: Le cancer du rectum est un problème important de santé publique aux implications majeures dans le domaines économique et social, dont le traitement de oncologique, celui chirurgical, mais aussi celui médical, implique des changements constants et des améliorations, qui ont pour objectif la préservation de la qualité de vie dans les conditions optimales d'oncologie. Dans le traitement complex de l'oncologie et le traitement chirurgical de n'importe quel type de cancer, la préservation de l'organe représente un succès thérapeutique. Pour les patients ayant un néoplasme rectal bas il est évident que la résection antérieure avec la préservation du sphincter (PS), lorsque c'est possible, attribue la plupart du temps une meilleure qualité de vie, avec une morbidité réduiteque dans le cas de la résection secondaire abdomino-périnéale et sans compromettre le résultat de l'oncologie.
Matériel et méthode: Pour réaliser cette analyse, la documentation a été révisée et les articles publiés entre les années 2005-2015 qui sont pertinents à la question en discussion, ont été étudiés.
Résultat de recherche: Il y a des études encourageants en ce qui concerne l'obtention de meilleurst aux de PS, selon le protocole d'irradiation préopératoire utilisé: courteou longue durée, avec ou sans chimiothérapie, avec un intervalle post thérapeutique court/ long jusqu'au moment opérateur. Le rôle de la radiothérapie périopératoire dans le traitement du cancer rectal résécable est évident en ce qui concerne la diminution des récidives locales, par rapport aux résections chirurgicales radicales sans irradiation. L'ajout de la radiothérapie a eu pour conséquence une amélioration significative du contrôle local, une réduction de la toxicité, mais sans réduire la mortalité globale et sans augmenter le nombre de résections avec le PS.

Correspondence address: *Dan Nicolae Păduraru, MD, PhD*
General Surgery and Emergency Clinic III, University Emergency Hospital Bucharest, Romania
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
e-mail: dan.paduraru.nicolae@gmail.com

Under certain conditions it may facilitate the resection procedure with SP. Further studies are needed in order to evaluate the role of chemoradiotherapy (CRT) in "sphincter sparing surgery", in the surgical treatment of rectal cancer.
Key words: rectal cancer, sphincter preservation (SP), total mesorectum excision (TME), chemoradiotherapy (CRT), local recurrence, brachytherapy

Conclusions: Le traitement du cancer du rectum nécessite une gestion multidisciplinaire continue, permettant d'ajuster en permanence une multitude de stratégies thérapeutiques pour chaque cas en particulier. La thérapie néoadjuvante est un élément indispensable dans l'algorithme de traitement et l'amélioration du résultat oncologique doit être le principal objectif. Dans certaines conditions celle – ci peut faciliter la résection avec le PS. Des études supplémentaires sont nécessaires pour évaluer le rôle de la radiochimiothérapie (RCT) dans "chirurgie de préservation du sphincter", dans le traitement chirurgical du cancer du rectum.
Mots clés: cancer du rectum, la préservation du sphincter (PS), excision totale du mésorectum (ETM), radiochimiothérapie (RCT), récidive locale, curiethérapie

INTRODUCTION

Colorectal cancer is globally the third leading cause of malignancy in men, following prostate cancer and lung cancer and the second in women, after breast cancer, with 1.4 million new cases and a total of 693,900 deaths estimated in 2012 [1].

The incidence and prevalence of this malignant location remain appreciable even if the absolute and relative number of patients seems to have decreased over the last 20 years, by implementing screening programs and by risk factor modification.

In 2015, the American Cancer Society (ACS) reported an annual decrease in the number of colorectal cancer disease in America of 4.3% between 2007-2011, for population over 50 years, but also an increase in the incidence of 1.8% per year among adults under 50 years of age [2].

In the European Union colorectal cancer incidence was estimated at 345,346 cases (13.1%) and the total number of deaths caused by this pathology was 150,000 (11.9%) in 2012. Rectal cancer is responsible for 35% of the overall incidence of malignant colorectal tumors, which means 15 to 25/100,000 inhabitants per year, and the mortality is 4-10/100,000 inhabitants, higher among men [1].

The number of disease cases varies greatly depending on the geographical area, the manner of addressing the population and on the high variability of associated risk factors [3].

Mortality from colorectal cancer has decreased in the past 20 years in most countries due to the implementation of programs for active prevention and detection, to a decrease in the prevalence of risk factors and to constant improvements made in respect of the investigation methods and multidisciplinary treatment [4].

In our country, the frequency of colorectal cancer is increasing, annually occurring an average of 2,000 patients. Incidence and mortality have doubled in the last 20 years due to: change of living and working conditions, decreased death rates and increased average lifespan of the population, determination of causes of death and improvement of statistical reporting. Less than 3% of cases occur in persons younger than 40 years; the number of illnesses increase exponentially for persons over 45 years and double with each life decade [5].

According to data from GLOBOCAN, the International Agency database for Research on Cancer (IARC), in 2012, 10.256 new cases of colorectal cancer were estimated in Romania, which corresponds to an incidence of 13%, with ASR(W) (age-standardised rate) of 26.4. The total number of deaths in this pathology was 5675 cases and for survival at five years, 24.170 patients, without statistically significant differences between the sexes [6].

Epidemiological data and the evolutionary potential make this malignancy an important public health issue with many implications at the social, economic and medical level. Rectal cancer remains a leading cause of cancer mortality in the general population, with all progress made in recent decades with regards to image and histopathological diagnosis and complex oncological treatment.

MATERIAL AND METHOD

In order to elaborate this research, a systematic research was conducted on the last decade literature, by accessing databases and websites such as: Cochrane Central Register of Controlled Trials, iarc.org, jco.ascopubs.org, pubmed.gov. Assessment of published articles was carried out over a period of six months. Analysis was performed using a combination of keywords: rectal cancer, SP, TME, CRT, local recurrence, brachytherapy.

Articles from the period of 2005-2015 were reviewed and analyzed.

Special attention was given to statistical processing of data, their relevance, excluding articles the information of which we deemed insignificant for what we wanted to analyze or results were similar to those already existing.

General information

Accurate preoperative evaluation is crucial to determine the treatment plan in current approach to rectal cancer. A multidisciplinary team consisting of a surgeon, gastroenterologist, pathologist, oncologist, radiologist, is essential in obtaining optimal results in treating this complex but curable type of cancer.

Treatment guides that are generally accepted, based on the role and effectiveness of various radiochemotherapeutic and surgical strategies serve as a starting point in the reasoning, but the treatment of rectal cancer remains strongly

individualised. Multidisciplinary management must be customized for each patient with rectal cancer and treatment protocol recommendation must be accepted by both surgeon and patient.

The modern treatment of rectal cancer includes presently three procedures: surgery, radiotherapy and chemotherapy, which aim, ideally, at the removal of the primary lesion and distant metastases without co-morbidities and mortality associated to the therapy, with preserving urinary, sexual and intestinal functions, and hence preserving life quality. Various therapeutic strategies aim at eradication of marginal malignant cells as well, in the discontinuous tumor areas in the pelvis, lymph nodes or metastatic regions, thus obtaining a good local control and keeping the disease away.

Within the multidisciplinary management of rectal cancer, standardized surgery remains the main curative therapy.

Historically, surgery for rectal cancer as the only method of treatment is associated with a high risk of local recurrence and systemic dissemination. Furthermore, abdominoperineal amputation is indicated for 10%-40% of patients, with permanent stoma at the time of diagnosis [7].

After the introduction in 1982 by R.J. Heald of the total mesorectum excision concept as radical oncology surgical technique based on embryological development and anatomy of rectum fascial plans, the "surgical gold standard" is represented by the tumor resection associated with total mesorectum excision and preservation of the appropriate functionality of the sphincter apparatus [8].

Management of patients with rectal cancer has improved significantly over the years, by improving surgical techniques, increasing performance of imaging methods, developing neo and/or adjuvant CRT strategies, improving evaluation and histopathology reporting; one of the objectives is, alongside survival, better quality of life (QOL), by lowering the lower limits of resection and applying a "sphincter saving procedure", as a result of „down-sizing" and „down-staging" of the tumor, without compromising the oncological radicality of the surgery.

Introducing TME has led to improved local control (rate of local recurrence below 5%) and improved survival rate, as well as to lower abdominal-perineal resection rate; however, in order to avoid associated significant postoperative complications and morbidity, the accurate technical execution of TME is essential in achieving the intended results [9].

Both the rate of local recurrence and quality of life are influenced by factors related to tumor, treatment, patient and to the quality of the surgery, which makes rectum cancer surgery a laborious surgery which must be performed by practitioners trained in specialized centers; the oncologic outcomes are improved and postoperative complications fewer, as experience is gained [10].

Most surgeons consider that lower rectal tumors located up to 6 cm from the anocutaneous line, invading the sphincter apparatus, or bulky tumors in an obese patient with narrow pelvis require abdominoperineal resection [7].

In general, organ preservation is a therapeutic success in the surgical oncology complex treatment of any type of cancer.

For patients with low rectal cancer it is obvious that anterior resection with SP, when feasible, most often leads to better quality of life, morbidity rate lower than that secondary to abdominal-perineal resection and it does not compromise the oncological outcome.

The finding that rectal adenocarcinoma usually does not extend distally to the rectal wall has allowed the reconstruction by means of anastomosis even for ultra-low tumors; 2 cm distal to the macroscopic edge of tumor were deemed sufficient [11]. According to some studies, in motivated and informed patients, with good preoperative functionality of the sphincter complex, a safety oncology margin of just 1 cm might be taken into consideration, should it be technically possible [12].

Debates

In order to obtain a R0 type surgical resection, while maintaining the functionality of the sphincter complex, CRT neoadjuvant treatment has become the general recommendation to treat patients with locally advanced rectal cancer, i.e., stage II/III [13].

The following question comes up: is it possible that neoadjuvant radio/chemoradiotherapeutic treatment with or without induction chemotherapy may improve the sphincter-preserving rate and at the same time maintain oncological outcome in anterior resections for ultra-low rectal tumors, threatening the sphincter complex, by reducing tumor volume and stage? Only randomized studies can provide an objective answer to this question [14].

The decision to assess the tumor, in terms of tumor size and location, relative to the dentate line and to decide on the type of surgery, before or after the response to neoadjuvant therapy, is also controversial. Many specialists continue to treat patients with the benchmark data obtained by magnetic resonance imaging (MRI) pretreatment CRT [15].

CT or MRI imaging evaluation of rectal cancer and pretherapeutic staging of the disease have allowed the use of radiochemotherapy as neoadjuvant treatment with superior results in terms of oncological benefit and toxic side effects, compared to treatment after surgery [16].

There are studies that provide encouraging information regarding obtaining better rates of SP, depending on the preoperative protocol of radiation used: short or long, with/without chemotherapy, with long/short post-therapeutic interval until surgery.

The Lyon R90-01 randomized study has evaluated the effect of the interval between the preoperative radiotherapy and surgery. It showed that a longer interval of 2 weeks after completing radiotherapy (RT) increases the chance of favorable reconversion of the tumor stage, without altering toxicity or local recurrence after 33 months follow-up. Furthermore, in 76% of patients operated between 4-6 weeks after RT it was possible to perform a "sphincter sparing" procedure compared to 68% of patients who underwent surgery after a shorter period of time (two weeks) [17].

Subsequently, another randomized study of the same group (Lyon R96-02) has showed that administration of a boost dose of endocavitary contact radiotherapy to the

external radiation regimen may increase complete clinical response and thus may improve the SPchance from 44% to 76%. The limitations of this study lie in the fact that it includes only 88 patients and 6 of them were administered brachytherapy as well, the selection being made arbitrarily [18].

Despite these deficiencies, both studies provide data for using high irradiating doses preoperatively and for postponing surgery in order to increase the SPchances.

Several studies have examined the impact of increasing the interval from CRT completion until surgery, but without obtaining comparable results with Lyon R90-01 study.

The increase of this interval was associated with improved complete pathologic response rate, and "down-staging" the tumor [19], without negatively impacting survival [20], but also without changing rates of resection and sphincter preservation. The extension of the free treatment interval is not yet correlated with any clinical benefit [21].

Three randomized studies have tried to answer the following question: preoperative or postoperative CRT? It is the case of the German study CAO/ARO/AIO 94 and INT 0147 and NSABP R0-3, American studies.

The German study CAO/ARO/AIO 94 of 2004 randomized 823 patients with locally advanced rectal cancer (stage T3/T4/N+), comparing pre and postoperative CRT effects. Surgical treatment consisted of TME in all cases and was followed by chemotherapy in both groups of patients. A significant 6% decrease in local recurrence rate was found in the group that received preoperative CRT compared to the group who was treated by chemo-radio postoperatively, whose percentage was 13% and the toxic effects were more pronounced. However, overall survival was not different [16]. Secondary to these main findings was the effect on the rate of sphincter preservation unit in the two groups of patients: a statistically significant difference of about 20% for the group receiving neoadjuvant CRT was found.

The follow-up of this trial in 2012 further showed reduced local recurrence in a similar manner, the incidence of long-term toxicity less in favor of patients treated preoperatively, but no impact on survival or on the distant disseminations [22].

The American trial National Surgical Adjuvant Breast and Bowel Project R-03 (NSABP R-03) recruited 267 patients between 1993 and 1999, and tried first to determine the right moment for administering CRT, preoperatively or postoperatively, in terms of overall survival (OS) and disease-free survival (DFS). Further information referred to the percentage of surgical resections with SP and local recurrence rate. A significant improvement in DFS in patients preoperatively treated with chemo-radio therapy was found (after an average follow-up after 8.4 years), patients for whom SP was 10% higher compared to the group receiving adjuvant treatment (44% versus 34%), but without increasing local control [23].

Neither the German study (CAO/ARO/AIO 94) nor the American trial (NSABP R-03) were not conducted to particularly analyze the modification of the SPrate under the influence of multimodal neoadjuvant therapy, which is why existing evidence is considered unclear, and the role of CRT in achieving tumor reduction so as to optimize resection procedures and sphincter preservation is controversial. (Table 1)

The Polish trial brings forth results contrary to those achieved by the German trial; the Polish trial compares the use of short-course radiation therapy (SCRT) as neoadjuvant-treatment versus CRT. There were no reported differences in terms of local recurrence, disease-free survival or overall survival. However, although there has been a clear improvement in tumor response in the group receiving CRT, the SP rate has not changed. An explanation for this could be: surgeons in this study were asked what type of resections they would perform before starting the radiation treatment; it is possible that due to oncological dogmatic reasons, their option might not have changed after completing neoadjuvant treatment [24].

The role of preoperative radiotherapy in the treatment of resectable rectal cancer is obvious in the decrease of local relapses, compared to the radical surgical resections without irradiation.

Several randomized trials have compared outcomes of

Table 1

Trial	Duration	No of patients	Therapeutic options	Results			
				SP	LR	DFS	OS
Lyon trial R90-01	1991-1995	201	RT and TME in 6-8 weeks v. RT and TME in 2 weeks.	76% v. 68%	No changes after 33 months	No changes after 33 months	No changes after 33 months
Lyon trial R96-02	1996-2001	88	EBRT+CXR and TME v. EBRT and TME	76% v. 44%	No changes	92% v. 88% after 2 years	90% la 2 ani
German trial CAO/ARO/ AIO 94	1995-2004	823	CRT and TME v. TME and CRT	35% v. 18%	7.1% v. 10.1% after 10 years	68.1% v. 67.8% after 10 years	59.6% v. 59.9% after 10 years
Polish trial	1999-2004	316	SCRT and TME v. CRT and TME	61.3% v. 58.3%	11% v. 16.5% after 5 years	58.4% v. 55.6% after 4 years	67.2% v. 66.2% after 4 years
NSABP R-03	1993-2003	267	CRT and TME v. TME and CRT	44% v. 34%	10.7% after 5 years	64.7% v. 53.4% after 5 years	74.5% v. 65.6% after 5 years
Dutch trial	1996-1999	1861	SCRT and TME v. TME	No changes	5.6% v. 10.9%	_	64.2%v. 63.5% after 5 years

EBRT: preoperative external-beam radiotherapy; CXR: contact x-ray; RT: radiotherapy; TME: total mesorectal excision; CRT:chemoradiotherapy; SCRT: short course of radiotherapy; LR: local recurrence; DFS: disease free survival; OS: overall survival; SP: sphincter preservation

surgery with/without preoperative radiotherapy. However, none of them reported differences in rates of sphincter complex preservation. The publication of results of the Swedish trials (The Swedish Rectal Cancer Trial - 1997) and Dutch trial (Dutch Colorectal Cancer Group - 2001), with long-term follow-up on patients, for 15 years and respectively 10 years has shown the benefit of using SCPRT, followed by radical resection, especially for resectable rectal cancers with circumferential margin of negative resection (CRM -) in terms of reducing the rate of local recurrence, increasing cancer-specific survival, but also increasing overall survival [25].

Adding radiotherapy triggered a significant improvement in local control, reduced toxicity, but did not reduce overall mortality and did not increase the number of resections with SP.

The results of randomized trials highlight the advantages of CRT versus RT as neoadjuvant treatment in locally advanced rectal cancer. The superiority of this treatment protocol lies in the optimization of local control of the disease and improvement of systemic control, by increasing pathological complete response rates (pCR), increasing R0 resections, reduction of local recurrence, eradicating micrometastases and improving specific survival of cancer (66% versus 53 % at 5 years) [26].

Although some studies support a favorable role of RT/CRT on the rate of SP, this has not been confirmed in two meta-analyzes: retrospective Cohrane analysis in 2007 [27] and Bujko, K□pka, Michalski 2006 [28] meta-analysis.

In addition, recent Cochrane meta-analysis in 2012 and 2013 of six and respectively five randomized trials have shown that adding chemotherapy to radiotherapy treatment before surgery of rectal tumors in stages II/III has a beneficial effect in terms of reducing local recurrence, by increasing radiosensitivity of tumor tissue, but without improving survival, sphincter preservation and without reducing toxicity [29].

Studies showing the effect of treatment type on the PS rate in locally advanced rectal cancer

Conclusion

The role of preoperative CRT is not currently proven in fostering resections with sphincter preservation, which leads to the conclusion that the main aim of the neoadjuvant treatment should be local and distant control of neoplastic disease and not "sphincter sparing". Improvement of tumor stage, following neoadjuvant CRT and reduced tumor size may support, under certain conditions, the indication of anterior resection with sphincter preservation.

The administration in the neoadjuvant CRT protocol of a boost dose of contact X-ray radiation therapy has been shown in some studies as beneficial for surgery treatment with sphincter preservation. Brachytherapy may increase the likelihood of anal sphincter preservation for tumors in the lower 2/3 of the rectum, acting through tumor "down staging" and "down sizing".

There are also studies showing that the tumoricidal effect of radiation is proportional to the free interval until the surgery. SPand pCR rate thus becomes higher if post CRT interval is greater (between 5 and 12 weeks).

In the lower rectal cancers that threaten sphincter complex, reducing tumor stage by neoadjuvant CRT can be used for performing a low anterior surgical resection while preserving the sphincter complex. However, existing data so far that mainly analyze the effects of CRT in facilitating resections with SP are few and the role of CRT remains controversial.

Multidisciplinary approach to patients with rectal cancer is essential, accurate preoperative assessment is the key, and treatment should be individualized depending on the particularities of each case.

Therefore, in formulating therapeutic reasoning, decisions for each step must be taken not only depending on one goal (survival or sphincter conservation, for example), but in relation to these four objectives: local recurrence, disease-free survival, overall survival QOL.

The role of surgery and of the surgeon in the therapeutic complex and in the multidisciplinary team should be reconsidered.

Paradigm shift for the surgeon implies the change of the center of gravity of the surgical objective from the desired"sphincter sparing" to a balancing perspective by introducing three new objectives: QOL, DFS, OS.

In any case, the need to obtain R0 resection type must remain a priority.

References

1. Torre, L., Bray, F., & Siegel, R. e. (2015). Global Cancer Statistics 2012. CA CANCER J CLIN, 65, 87-108.
2. ACS. (2015). Cancer Facts & Figures 2015. Atlanta: American Cancer Society.
3. Beck, D. (2015). Epidemiology and Burden of Rectal Cancer. In W. Longo, V. Reddy, & R. Audisio, Modern Management of Cancer of the Rectum second edition (pp. 13-19). London: Springer.
4. Bosetti, C., Levi, F., & Rosato, V. e. (2011). Recent trends in colorectal cancer mortality in Europe. Int J Cancer , 180-191.
5. Dragomir, C., Scripcariu, V., & Dajbog, E. (2009). Cancerul de colon . In Tratat de chirurgie vol. IX Chirurgie Generala partea a II-a (pp. 226-269). Bucuresti: Editura Academiei Române.
6. Ferlay, J., Soerjomataram, I., & Ervik, M. e. (2013, 10 09). Fact Sheets by Population. Retrieved 10 09, 2015, from GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012: www.iarc.fr.
7. Glynne-Jones, R., & Harisson, M. (2013). Preoperative radiotherapy and chemoradiotherapy for rectal cancer. In B. Moran, & R. Heald, Manual of Total Mesorectal Excision (pp. 87-102). Boca Raton: CRC Press.
8. Heald, R., Husband, E., & Ryall, R. (1982). The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? Br. J. Surg., 69, 613-616.
9. Heald, R., Moran, B., & Ryall, R. e. (1998). Rectal cancer: the Basingstoke experience of total mesorectal excision. Arch.Surg. , 894-899.
10. Wibe, A., Møller, B., & Norstein, J. e. (2002). A national strategic change in treatment policy for rectal cancer-implementation of total mesorectal excision as routine treatment in Norway. Dis Colon Rectum , 857-866.
11. Moran, B. (2013). Total mesorectal excision for rectal cancer. In B. Moran, & R. Heald, Manual of Total Mesorectal Excision (pp. 103-123). Boca Raton: CRC Press.
12. Karanjia, N., Schache, D., & North, W. (1990). Close shave'

in anterior resection. Br J Surg. , 510-512.
13. Glynne-Jones, R., Harrison, M., & Hughes, R. (2013). Challenges in the neoadjuvant treatment of rectal cancer: balancing the risk of recurrence and quality of life. Cancer Radiother., 675-685.
14. Minsky, B. (2002). Sphincter preservation for rec- tal cancer: Fact or fiction? . J Clin Oncol , 1971-1972.
15. Codd, R., & Sagar, P. (2015). The Surgeon's Perspective on Neoadjuvant Chemoradiation for Rectal Cancer. In Modern Management of Cancer of the Rectum Second Edition (pp. 97-108). London: Springer.
16. Sauer, R., Becker, H., & Hohenberger, W. e. (2004). Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. , 1731-1740.
17. Francois, Y., Nemoz, C., & Baulieux, J. e. (1999). Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol., 2396-2402.
18. Gerard, J., Chapet, O., & Nemoz, C. e. (2004). Improved Sphincter Preservation in Low Rectal Cancer With High-Dose Preoperative Radiotherapy: The Lyon R96-02 Randomized Trial. J Clin Oncol , 2404-2409.
19. Moore, H., Gittleman, A., & Minsky, B. e. (2004). Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. . Dis Colon Rectum , 279-286.
20. Moore, H., Gittleman, A., & Minsky, B. e. (2004). Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. . Dis Colon Rectum , 279-286.
21. National Comprehensive Cancer Network. (2014, 09 14). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Rectal Cancer Version 2.2015. Retrieved 09 14, 2015, from National Comprehensive Cancer Network: www.nccn.org.
22. Sauer, R., Liersch, T., & Merkel, S. e. (2012). 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 , 1926-1933.
23. Roh, M., Colangelo, L., & O'Connell, M. e. (2009). Preoperative Multimodality Therapy Improves Disease-Free Survival in Patients With Carcinoma of the Rectum: NSABP R-03. J Clin Oncol , 5124-5130.
24. Bujko, K., Nowacki, M., & Nasierowska-Guttmejer, A. e. (2004). Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol. , 15-24.
25. Folkesson, J., Birgisson, H., & Pahlman, L. e. (2005). Swedish Rectal Cancer Trial: Long Lasting Benefits From Radiotherapy on Survival and Local Recurrence Rate. JOURNAL OF CLINICAL ONCOLOGY , 5644-5650.
26. Braendengen, M., Tveit, K., & Berglund, A. e. (2008). Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. , 3687-3694.
27. Wong, R., Tandan, V., De Silva, S., & Figueredo, A. (2007). Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. Cochrane Database Syst Rev. , CD002102.
28. Bujko, .., Kepka, L., Michalski, W., & Nowacki, M. (2006). Does rectal cancer shrinkage induced by preoperative radio(chemo) therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol , 4-1.
29. De Caluwé, L., Van Nieuwenhove, Y., & Ceelen, W. (2013). Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. , CD006041.