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Evidence Based Case Report

Short-Course versus Long-Course Preoperative Radiotherapy in Rectal Cancer

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Abstract

Background Surgery is the mainstay therapy for colorectal carcinoma with curative intent, while radiotherapy and chemotherapy act as adjuvant or neoadjuvant therapy. The desicion for surgery depends on tumor resectability. Neoadjuvant radiotherapy, both short-course radiotherapy (SRT) or long-course radiotherapy (LRT) with or without concurent chemotherapy, is aimed to increase tumor resectability. This article compares advantages of SRT and LRT.
Method We designed a search filter using relevant synonyms for the domain: "rectal carcinoma", "resectable", "preoperative radiotherapy", and "short-course". Publications are retrieved from PubMed, Cochrane Library, and EBSCO using MESH terms and search terms in title and abstract fields. Articles' titles and abstracts from search result are screened for relevance. Eligible articles are selected based on inclusion and exclusion criterias. Selected articles are critically appraised for methods validity.
Result Six articles are included in our study, consists of four randomized clinical trials and two metaanalyses.
Conclusion SRT is as effective as LRT with or without chemotherapy in terms of overall survival, disease free survival, local recurrence rate, disease metastasis rate, free resection rate, and grade 3-4 toxicity. LRT with or without chemotherapy showed superiority in increasing pathological complete response rate and sphincter preservation rate. SRT is a better choice in centers with a long waiting list.
Keywords: colorectal carcinoma, preoperative radiotherapy, radiotherapy

Clinical case

A 58 year-old female patient was referred by a digestive surgeon with stage T3N2M0 well differentiated rectal carcinoma to receive short-course preoperative radiotherapy. The patient wondered whether if she would get more benefit from short-course or long-course radiotherapy.

Background

Colorectal carcinoma is the third most common malignancy in the world and the second cause of death among all malignancies in the United States. From the 2012 Globocan data, the incidence of colorectal cancer in Indonesia is 12.8 per 100,000 adult population, with mortality 9.5% of all cancer cases.

Management of colorectal cancer involves multidisciplinary team including gastroenterologist, digestive surgeon, and radiation oncologist. Treatment and setting depend on several factors, such as cancer stage, histopathology, possible side effects, patient overall condition, and patient preference. Surgical therapy is the major modality in rectal cancer with curative goal,

while radiotherapy and chemotherapy act as adjuvant therapy.[1-3]

Locoregional recurrence in rectal cancer cases of disease is mainly affected by involvement of tumor at circular resection margin, positive lymph nodes, and extramural blood vessel invasion. To reduce local recurrence, radiation and chemotherapy adjuvant therapy may be given pre- and post-surgical intervention. Goals of preoperative radiotherapy are:[4]

1. reduce risk of local recurrence, especially in patients with poor histopathological prognosis;
2. increase the possibility of sphincter preservation procedures;
3. increase the rate of resectability in tumors that are locally advanced or unresectable; and
4. reduce the number of viable tumor cells thereby reduce the possibility of contamination and spread of tumor cells through the bloodstream during surgery.

There are two modalities in providing preoperative radiation:[3,5,6]

1. short-course radiation (SRT) with a dose of 5×5 Gy followed by immediate surgery within several days, and
2. long-course radiation (LRT) with a total dose of 45-50.4 Gy in 25-28 fractions with or without chemotherapy, followed by surgery after 4-8 weeks.

Although the radiation technique is similar, the fractionation and surgery span time are different. The advantage of SRT is shorter preoperative therapy duration, while the limitation is less useful in downsizing the primary tumor because surgery is performed in just a short time after radiation. Nevertheless, some studies have shown that SRT tumor downsizing can be achieved when surgical action is delayed up to 6-8 weeks after short radiation is given.[3,5,6]

When LRT is used, it should be followed by concomitant chemotherapy to increase the possibility of primary tumor downsizing, achieve pathologic complete response (pCR), increase resectability, and preserve sphincter function in low-lying tumor cases, as well as lower local recurrence risk and increase long -term survival.[3,5,6]

The ideal preoperative approach is still a controversy until today. SRT proponents argue that it could improve patient comfort and reduce cost compared with LRT, while LRT proponents emphasize lower surgery morbidity and higher possibility of sphincter preservation.[3,5,6]

Clinical question

In a patient with resectable rectal carcinoma undergoing preoperative radiotherapy, is there any difference in local control rate and disease-free survival between short-course radiotherapy and long-course radiotherapy with or without concurrent chemotherapy?

Searching methodology

We designed a search filter using relevant synonyms for the domain: “rectal carcinoma”, “resectable”, “preoperative radiotherapy”, and “short-course”. We retrieved relevant publications in PubMed, Cochrane Library, and EBSCO using MESH terms search terms in title and abstract fields. Our search yielded 210 records in PubMed, 34 in Cochrane Library, and 601 in EBSCO (Table 1).

We found 109 eligible study from PubMed, 33 from Cochrane, and 43 from EBSCO. Inclusion criterias are RCT, meta-analysis, or systematic review studies, article published in the last 10 years, written in English, and its abstract is readily available. The exclusion criterias are animal study and descriptive study. Title and abstract of all retrieved records were screened to retrieve direct comparison between SRT and LRT. We continued assessing sixteen studies’ full text and excluded nine because of article’s content (review, study protocol, consensus), ongoing trial, interim analysis, and descriptive study. Seven articles were critically appraised (Table 2 and 3). One article was excluded because of inadequate study validity.

Result

Bujko et al[7] performed a concealed, randomized trial with intention to treat analysis to assess overall survival and local control rate between SRT and LRT plus chemotherapy in 312 patients diagnosed with stage T3 or T4 resectable rectal cancer. SRT group received preoperative irradiation (five fractions of 5 Gy) with total mesorectal excision (TME) performed within 7 days, while LRT group received chemoradiation (50.4 Gy in 28 fractions, 1.8 Gy per fraction, plus bolus 5-fluorouracil and leucovorin) and TME 4-6 weeks later. They showed that neoadjuvant chemoradiation did not increase overall survival (OS), local control, or late toxicity compared with SRT alone ($p>0.05$).

Table 1. Search terms used in online database

Search date: 6th November 2017

Database	Search term	hits
PUBMED	#1 AND #2 AND #3 AND #4 AND #5 AND (#6 OR #7)	210
Cochrane	([Rectum] this term only OR rectum OR rectal) AND ([Neoplasms] explode all trees OR rect* neoplasm$ OR rect* cancer$ OR rect* carcinoma$ OR rect* tumor$) AND (resectab* OR operab* OR treateb*) AND (preoperat* OR presurg* OR neo?adjuvant) AND ([Radiotherapy] explode all trees OR *radiation therapy OR *radiation OR teletherapy) AND (Short* OR hypofraction*) AND (long* OR convention*)	34
EBSCO	(((((MM "Rectum") OR *rectum OR *rectal) AND ((MM "Neoplasms") OR (MM "Rectal Neoplasms") OR cancer$ OR *carcinoma$ OR neoplas* OR malignan* OR tumor$) AND (preoperat* OR presurg* OR neoadjuvant OR neo?adjuvant) AND ((MM "Radiotherapy") OR (MM "Radiotherapy, Adjuvant") OR radiotherapy OR *radiation therapy OR *radiation OR teletherapy)) NOT (benign OR adenoma$ OR polyp$)) NOT unresectable) AND (short* OR hypofraction*)	601

PUBMED search terms		Term
#1	(rectum[MeSH Major Topic] OR *rectum[Title/Abstract] OR *rectal[Title/Abstract])	Rectum
#2	(Neoplasms[MeSH Major Topic] OR Rectal Neoplasms[MeSH Major Topic] OR cancer$[Title/Abstract] OR *carcinoma$[Title/Abstract] OR neoplas*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor$[Title/Abstract])	(rectal) cancer
#3	(preoperat*[Title/Abstract] OR presurg*[Title/Abstract] OR neo? adjuvant[Title/Abstract])	Preoperative
#4	(radiotherapy[MeSH Major Topic] OR Radiotherapy, Adjuvant[MeSH Terms] OR radiotherapy[Title/Abstract] OR *radiation therapy[Title/Abstract] OR *radiation[Title/Abstract] OR teletherapy[Title/Abstract])	Radiotherapy
#5	(Short*[Title/Abstract] OR hypofraction*[Title/Abstract])	Short-course
#6	(randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])))	RCT
#7	systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal:__jrid21711] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]	Meta-analysis

Erlandson et al[8] conducted a non-inferiority RCT. They grouped 385 patients in three-arm randomization: short -course radiotherapy 5×5 Gy with early surgery (SRT), short-course radiotherapy 5×5 Gy with delayed surgery (SRT-delay), and long-course radiotherapy 25×2 Gy with delayed surgery (LRT-delay). The others 455 patients were put in two-arm randomization to compare the outcomes between SRT and SRT-delay. In both three-arm and two-arm randomization, no significant difference were observed regarding time to local recurrence and OS.

Latkauskas et al[9] conducted a RCT comparing preoperative conventional chemoradiotherapy (50 Gy) and SRT (25 Gy) both with delayed surgery in patients diagnosed with stage II and stage III resectable rectal cancer. Type of surgery was conditional, but total mesorectal excision was mandatory. One-hundred-and-fifty patients were included in this trial. This RCT showed that there were no statistically significant difference in OS, downstaging, and pCR rate. But this RCT showed that three years disease free survival (DFS) was better in conventional chemoradiotherapy group (59% in SRT group vs 75.1% in CRT group,

p=0.022). Hazard ratio of local and distant cancer progression for SRT patients compared to CRT patients was 1.93 (95% CI 1.08 to 3.43).

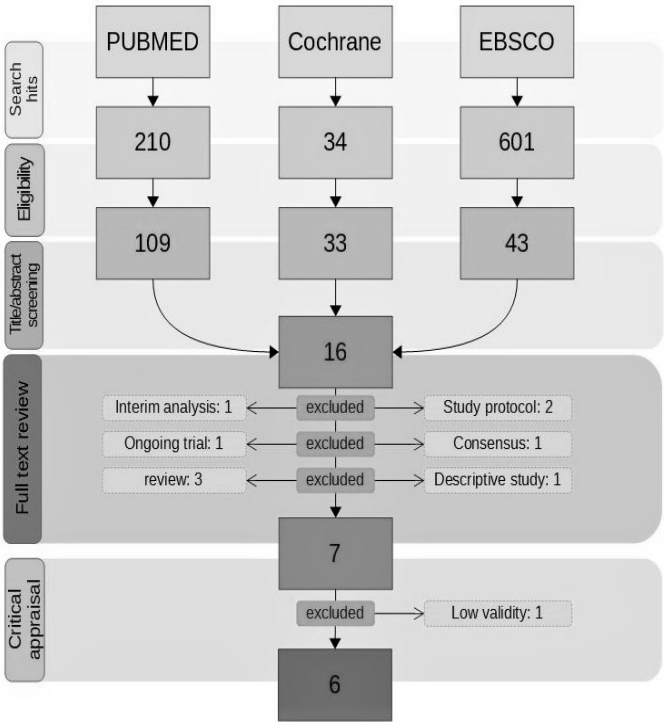

Figure 1. Literature search flow chart

Liu et al[10] conducted a meta-analysis on three RCT studies. The study yielded a total of 357 patients in pooled result. They compared SRT and LRT, both proceeded by delayed surgery. Sphincter preservation rate, local recurrence rate, grade 3-4 toxicity, R0 resection rate, and downstaging rate were not different statistically between two groups. Compared with short course radiotherapy, long course radiotherapy increased pCR rate.

Table 2. Critical appraisal of RCT studies

No. Author	Determinant	Outcome	Similar characteristics	Randomization	Concealment	Missing data	Intention-to-treat analysis	Blinded allocation	Blinded outcome assessment	Equal treatment
1. Bujko et al	1. SCRT 2. LCRT	1. OS 2. Local recurrence	+	+	?	0	+	-	?	+
2. Erlandsson et al	1. SCRT plus early surgery 2. SCRT plus delayed surgery 3. LCRT plus delayed surgery	1. Local recurrence 2. Death	+	+	+	0	+	-	+	+
3. Guckenberger et al	1. SCRT 2. LCRT	1. Local control 2. DFS 3. OS	-	-	-	0	-	-	?	+
4. Latkauskas et al	1. SCRT 2. LCRT	1. Local recurrence 2. Death	+	-	?	0	-	-	?	+

Viani et al[11] conducted a meta-analysis and meta-regression on 21 RCTs published in 1975 to 2001, yielding 9,097 patients in pooled result. They compared two groups of sample, the one underwent preoperative radiation followed by surgical intervention, and the other surgery alone. The experimental group were further divided into four categories according to the applied biological effective dose (BED) and fractionation of preoperative radiotherapy. They showed that there were no statistically significant difference in mortality and local recurrence between low BED radiotherapy (≤30 Gy) compared to surgery alone (p>0.05). High BED (>30 Gy) SRT showed superiority compared to LRT in local recurrence rate (OR 0.38 [95% CI 0.32 to 0.46] vs 0.53 [95% CI 0.41 to 0.69]), but LRT showed better result in mortality rate (OR 0.77 [95% CI 0.61 to 0.99] vs 0.87 [95% CI 0.76 to 0.99]) and sphincter preservation (OR 0.65 [95% CI 0.48 to 0.88] vs 1 [95% CI 0.87 to 1.14]).

Table 3. Critical appraisal of meta-analyses

No. Author	Determinant	Outcome	RCT of interest	Finding methods	Individual trial validity assessment	Consistent result
1. Liu et al	1. SCRT 2. LCRT	1. Sphincter preservation 2. Local recurrence 3. Acute toxicity 4. R0 resection rate 5. Downstaging rate	+	+	+	+
2. Viani et al	1. RT with various BED and fractionation plus surgery 2. Surgery alone	1. Local recurrence 2. Overall mortality 3. Sphincter preservation	+	+	-	-
3. Zhou et al	1. SCRT 2. LCRT	1. Local recurrence 2. Disease free survival 3. Overall survival	+	+	+	-

Zhou et al[12] conducted a meta-analysis on 12 studies (four RCTs and eight non-RCTs). The study yielded total 2,187 patients in pooled result. They compared two groups of sample undergoing SRT with immediate surgery and LRT with delayed surgery. This meta-analysis show that there were no statistically significant difference in OS, DFS, local recurrence rate, distant metastasis rate, sphincter preservation rate, R0 resection rate and late toxicity (p>0.05). LRT increased pCR rate (RR=0.15, 95% CI 0.08 to 0.28, p<0.001) and grade 3-4 acute toxicity (RR=0.06, 95% CI 0.02 to 0.16, p<0.001).

Discussion

Most of the studies indicated no statistically significant difference between SRT and LRT in DFS and local recurrence,[7,8,10,12] but there are some contradictions. Meta-analysis by Viani et al showed that SRT was more superior in reducing local recurrence than LRT. This study shortfall was indirect comparison between SRT and LRT, not considering time span to surgery, lack of individual study validity assessment, and imbalance in pooled sample number.[11]

RCT conducted by Latkauskus showed that LRT gave better three-year DFS and less progression than SRT, but no difference in OS, downstaging, and pCR,[9] which is somehow contradictive. DFS has been validated as a surrogate endpoint of OS by showing strong correlation between both parameters.[13] LRT is more favorable in achieving pCR in meta-analysis by Liu et al and Zhou et al, but both study showed no difference in local reccurence.[10,12] pCR is linked with lower reccurence rate and better survival in breast cancer, but more research is needed to prove this in rectal cancer.[14,15]

Aside from our outcomes of interest, Viani et al showed LRT is better in sphincter preservation than LRT. Viani et al also showed that BED had to be accounted to achieve better outcome.[11]

Conclusion

SRT is as effective as LRT with or without chemotherapy in terms of DFS and local control rate. LRT showed superiority in increasing pCR and sphincter preservation rate.

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