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ORIGINAL ARTICLE

Non-operative treatment outcome for rectal cancer patient with clinical complete response after neoadjuvant chemoradiotherapy

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KEYWORDS
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Complete response;
Local excision;
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Summary *Background:* Among rectal cancer patients, some of good responders after neoadjuvant chemoradiotherapy (nCRT) are considered for non-operative treatments to avoid postoperative morbidities and permanent stoma. However, oncologic feasibility of non-operative treatment has not been fully understood.
Methods: From 2008 to 2017, we retrospectively reviewed patient's records who had lower or mid rectal cancer and diagnosed to clinical complete response by magnetic resonance imaging after nCRT. Clinical differences and oncologic outcomes were compared among Radical surgery (RS), Local excision (LE) and Wait-and-see (WS) group.
Results: Number of 129, 25, 15 patients included to RS, LE, WS groups. Local recurrence was frequent type of recurrence in both of LE and WS group (RS; 31.3%, LE; 80%, WS; 66.7%), and many patients in WS group omitted salvage treatment (RS; 75%, LE; 100%, WS; 33.3%). 5-years local-recurrence/disease-free survival rate (LRFS, DFS) between RS and LE were similar between each group, but WS showed significantly inferior outcomes than that of RS (LRFS; $p = 0.001$, DFS; $p = 0.001$). In multivariate analysis, WS protocol (OR; 7.163, 95% CI; 1.995–25.715) and cT4 stage (OR; 8.206, 95% CI; 1.596–42.198) were independent factors for LRFS.
Conclusions: Wait-and-see group showed high rate of rejection of salvage treatments for recurrence, and poor oncologic outcomes. However, recent low-level evidences reported favorable outcome of WS protocol when salvage treatment was followed after recurrence. It seems that the application of WS protocol should be postponed until the results of

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randomized-controlled trials are available. Local excision seems to be good alternative option to radical surgery when salvage treatment is followed.

1. Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision is considered the standard of care in the treatment of locally advanced rectal cancer. After nCRT, approximately 50%—60% of patients are down-staged, and tumor response has been shown to facilitate sphincter-saving surgery and deliver a favorable oncologic prognosis.[1—5] However, Radical surgery (RS) following nCRT is still associated with significant morbidities from post-operative complications.[6,7]

Because of these disadvantages from surgical treatments, non-operative treatment such as WS protocol have been studied for highly-selected patients expected to achieve pathological complete response (pCR) in order to enhance quality of life while maintaining acceptable oncologic results. However, the efficacy of Wait-and-see (WS) is controversial since previous studies have heterogeneity in study designs and treatment outcomes.[8—21] Therefore, we reviewed medical records of rectal cancer patients who had been diagnosed to clinical complete response (cCR) after nCRT, to investigate the treatment outcome of WS protocol.

2. Material and methods

2.1. Patient selection

We retrospectively reviewed our prospectively collected database of rectal cancer patients treated between January 2008 and December 2017. The study design was approved by the appropriate ethics review board, which waived the requirement for informed consent. Radiologic complete responders after nCRT without distant metastasis were included. Rectal cancer was defined as a tumor located $\leq$15 cm from the anal verge (AV). CRT was administered to patients with locally advanced mid to low rectal cancers (clinical diagnosis of T3, 4, or N+). nCRT consisted of 5-fluorouracil-based chemotherapy with concomitant long-course radiation (5040 cGy in 28 fractions). A cCR was defined as satisfying the following criteria, based on magnetic resonance imaging (MRI): (1) no residual tumor or residual fibrosis, and (2) no suspicious metastatic lymph nodes. The treatment approach and follow-up protocol were similar to our previous paper.[22]

2.2. Radiologic evaluation

MRI was performed 5—6 weeks after the completion of nCRT. All examinations were performed on a 3-T scanner (Magnetom TrioTim; Siemens Medical Solutions, Erlangen, Germany) with multiple phased-array body coils. The imaging protocol included axial and oblique T1-weighted images and axial, sagittal, coronal, and oblique T2-weighted images. Axial diffusion-weighted MRI scans were also acquired. MRI-assessed tumor response was assessed by either of two experienced radiologists, particularly based on the diffusion-weighted MRI. Initial readings of MRI scans were utilized to define cCR.

2.3. Treatment

Patients with cCR received one of three treatment protocols: RS, LE (local excision), or WS. The treatment plan was determined by consideration of the age, underlying disease, tumor height from the anus, and sphincter function, together with patient's choice. Basically, all patients were recommended for radical surgery, but local excision or wait-and-see was considered when sphincter-saving was not expected to be possible or if the patient refused radical surgery. RS was performed with curative intent 6—10 weeks after completion of radiotherapy. All patients in radical surgery group underwent standard total mesorectal excision and regional lymphadenectomy. LE was also performed 6—10 weeks after radiotherapy via a transanal approach under spinal or general anesthesia. Full thickness excision of the tumor or scar was performed. According to the final pathologic reports, tumors were restaged according to the 8th edition of the American Joint Committee on Cancer TNM staging system at the time the data were reviewed. Most patients who underwent surgery were recommended to receive 5-fluorouracil-based adjuvant chemotherapy regardless of the final pathology. Patients who followed a WS protocol were closely monitored without routine administration of adjuvant chemotherapy.

2.4. Follow-up

The patients who underwent RS were followed-up for 5 years at 6-month intervals, while the LE and WS groups were followed-up at 3-month intervals for 2 years and at 6-month intervals for the next 3 years. Follow-up examinations, including serum carcinoembryonic antigen, chest X-ray or computed tomography and endoscopy, were conducted on a semiannual basis and MRI and positron emission tomography were added when recurrence was suspected, in accordance with according the National Comprehensive Cancer Network guidelines.

2.5. Endpoints

The primary endpoint was local-recurrence-free survival (LRFS) and disease-free survival (DFS). All time to-event variables were calculated from the date of nCRT completion. LRFS was measured from the date of completion of radiotherapy to the date of LR or death. DFS was defined as

time to any recurrence, and measured from the date of completion of radiotherapy to the date of recurrence or death. Recurrence was determined by clinical and radiological examinations or by histological confirmation.

2.6. Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test, as well as linear analysis. Continuous variables were compared using the Mann–Whitney U test or the Kruskal–Wallis test. Survival rates were compared using the Kaplan–Meier method and log-rank tests, and Cox regression analysis was used for multivariate analysis. Results were considered significant at $p < 0.05$. Statistical analyses were conducted using SPSS software version 21.0 (IBM Inc., Armonk, NY).

3. Results

Over 10 years (2008–2017), 169 (14.8%) of 1140 rectal cancer patients had been diagnosed to cCR after nCRT. Patients were treated by RS (n = 129), LE (n = 25), and WS (n = 15). Median age was youngest in the RS group and tumor distance from the AV was lowest in the LE group. Pre- and post-nCRT CEA level and cT stage were not different among the three treatment groups, but cN stage was more frequently positive in the WS group. The median follow-up period was 48 (5–100), 30 (2–93), and 20 (2–56) months in the RS, LE, and WS groups, respectively ($p < 0.001$). pCR was achieved in 33.9% (n = 43) of patients in the RS group. Circumferential resection margin after RS and margin involvement status of LE was 2.3% and 8.0%, respectively ($p = 0.186$, Table 1).

WS group received less adjuvant chemotherapy and experienced more recurrences than other groups (RS; 12.4%, LE; 20%, WS; 40%, $p = 0.019$), but WS received less salvage treatment (RS 75%; LE 100%; WS 33.3%, Tables 2 and 3).

LRFS and DFS were similar between the RS and LE groups (LRFS; $p = 0.059$/DFS; $p = 0.067$), but the WS group had inferior outcomes to the RS group (LRFS; $p = 0.001$/DFS; $p = 0.001$). The 3-year and 5-year LRFS in the RS, LE, and WS groups was 95.6%, 78.6%, 53.8%, and 93.2%, 78.6%, 26.9%, respectively. The 3-year and 5-year DFS in the RS, LE, and WS groups was 89.6%, 72.9%, 55.5% and 85.9%, 72.9%, 27.8%, respectively. RS and LE shows similar survival outcomes, while WS had inferior survival outcome than RS (Fig. 1).

In univariate analysis, old age (>70 years), treatment protocol (WS), and cT4 stage were associated with LRFS. However, WS [odds ratio (OR), 7.163; 95% confidence interval (CI), 1.995–25.715; $p = 0.003$] and cT4 stage (OR, 8.206; 95% CI, 1.596–42.198; $p = 0.012$) were independent factors for LRFS in the multivariate analysis (Table 4).

Table 1 Baseline characteristics of patients.

	RS n = 129	LE n = 25	WS n = 15	p
Male sex	94 (72.9)	15 (60.0)	8 (53.3)	0.167
Age, years	63.8 (33–83)	73.0 (44–81)	74.0 (39–89)	<0.001
Distance from the AV, cm	4.67 (2.0–11.0)	3.50 (2.0–8.0)	4.29 (2.0–10.0)	0.014
Pre-CRT CEA, ug/ml	3.08 (0.20–45.61)	4.30 (1.10–123.04)	2.98 (0.84–6.42)	0.073
Post-CRT CEA, ug/ml	1.92 (0.25–10.02)	2.37 (0.90–7.72)	2.64 (0.60–4.41)	0.621
cT stage				0.085
cT1-2	8 (6.2)	2 (8.0)	3 (20.0)	
cT3-4	121 (93.8)	23 (92.0)	12 (80.0)	
cN stage				0.029
cN0	75 (58.1)	19 (76.0)	5 (33.3)	
cN+	54 (41.9)	6 (24.0)	10 (66.7)	
pT stage				0.104
pT0	46 (35.7)	12 (48.0)		
pT1-2	47 (36.5)	11 (44.0)		
pT3-4	36 (27.9)	2 (8.0)		
pN stage				
pN0	108 (86.4)			
pN+	21 (16.3)			
Pathologic CR	43 (33.9)	12 (48.0)		0.121
Positive CRM or resection margin	3 (2.3)	2 (8.0)		0.186
Adjuvant chemotherapy				<0.001
Performed	124 (96.1)	18 (72.0)	5 (33.3)	
Not performed	5 (3.9)	7 (28.0)	10 (66.7)	
F/u periods, Months	48 (5–100)	30 (2–93)	20 (2–56)	<0.001

Values are shown as n (%) or median (range).
RS: radical surgery/LE: local excision/WS: wait and see.
CEA: carcinoembryonic antigen/CRM: circumferential resection margin.

Table 2 Treatment after recurrence.

	RS n = 129	LE n = 25	WS n = 15	p
Recurrence	16 (12.4)	5 (20.0)	6 (40.0)	0.019
Recurrence type				0.096
Local ± distant	5 (31.3)	4 (80.0)	4 (66.7)	
Distant only	11 (68.8)	1 (20.0)	2 (33.3)	
NED periods (months, median)	22.5 (5–62)	15 (4–23)	16 (6–38)	0.272
Salvage treatment (yes)	12 (75.0)	5 (100)	2 (33.3)	0.137

RS: radical surgery/LE: local excision/WS: wait and see.

4. Discussion

We previously reported the unfavorable oncologic outcomes of LE and WS in rectal cancer patients who were suspected of having a cCR after nCRT from 2006 to 2011 (Table 5).[22] This study collected more data to better compare the oncologic outcomes of patients with cCR after nCRT. In this series, the oncologic outcome of LE was equivalent to RS, but WS still showed poorer survival outcomes. Despite the oncologic results of LE was similar with RS in this study, the recurrence pattern showed a predominance of local recurrence, similar to that observed after WS (Table 2). The higher incidence of local recurrence may be explained by the risk of remnant cancer cells and metastases in the mesenteric lymph nodes after LE and WS.

According to a previous report, the nodal sterilization rate (pN0 rate among cN + patients) after neoadjuvant chemotherapy was low, only 56%,[23] and the risk of remnant metastatic lymph nodes has been the basis of opposition to LE. Chang et al reported ypN+ was the independent factors for poor cancer-specific survival in the poor responder group (ypT3-4).[24] Park et al also investigated risk factors for oncologic outcomes of good responders (ypT0-2). But, interestingly, they reported ypT stage (ypT2) as an only independent factor for poor survival, not ypN + status. They reported significantly higher local recurrence rate of ypN + than ypN0 group, but 5-year recurrence-free survival was not different between 2 groups.[25] The rate of lymph node metastasis was about 20% in case of ypT2, which has resulted in poor survival outcome.[26,27] This study also

Table 3 Recurrences.

Tx		cStage	1st recur.	Time to Recur. (m)	Tx	Survival status	f/u months
RS	64/M	cT3N1	Local	15	Op,CTx	Alive	87
	76/F	cT3N1	Local + Distant	5	Op,CTx	Alive	17
	67/M	cT3N1	Local	38	refused	Alive	58
	73/M	cT3N0	Distant	24	Op,CTx	Alive (NED)	65
	70/M	cT3N0	Distant	62	CRT	Expired	68
	64/M	cT3N0	Distant	29	Op,CTx	Alive (NED)	100
	62/M	cT3N1	Distant	24	Op,CTx	Alive (NED)	81
	59/M	cT3N1	Distant	56	Op,CTx	Alive	79
	55/M	cT3N1	Distant	22	Op,CTx	Alive (NED)	30
	66/F	cT3N0	Distant	17	Op,CTx	Alive (NED)	57
	75/F	cT3N0	Distant	5	CTx	Expired	18
	77/M	cT3N1	Distant	18	refused	Alive	41
	66/M	cT2N1	Distant	11	Op	Alive (NED)	17
	73/M	cT3N0	Distant	18	refused	Alive	21
	81/F	cT3N0	Local	49	refused	Expired	55
	80/M	cT3N0	Local	24	CTx	Alive	26
LE	65/M	cT3N0	Local	15	Op	Expired	35
	64/M	cT1N1	Local	8	CTx	Expired	37
	79/F	cT3N0	Local	4	Redo LE, CTx	Expired	30
	63/F	cT3N0	Distant	15	CTx	Expired	36
	73/M	cT3N1	Local	23	Op	Expired	60
WS	72/M	cT3N1	Local + Distant	38	refused	Expired	47
	78/F	cT4N0	Local	12	Op,CTx	Alive	26
	39/F	cT3N1	Distant	7	refused	Expired	7
	80/M	cT3N1	Distant	32	refused	Expired	33
	69/F	cT4N1	Local	6	CTx	Expired	11
	80/M	cT3N1	Local	20	refused	Alive	20

RS: radical surgery/LE: local excision/WS: wait and see.

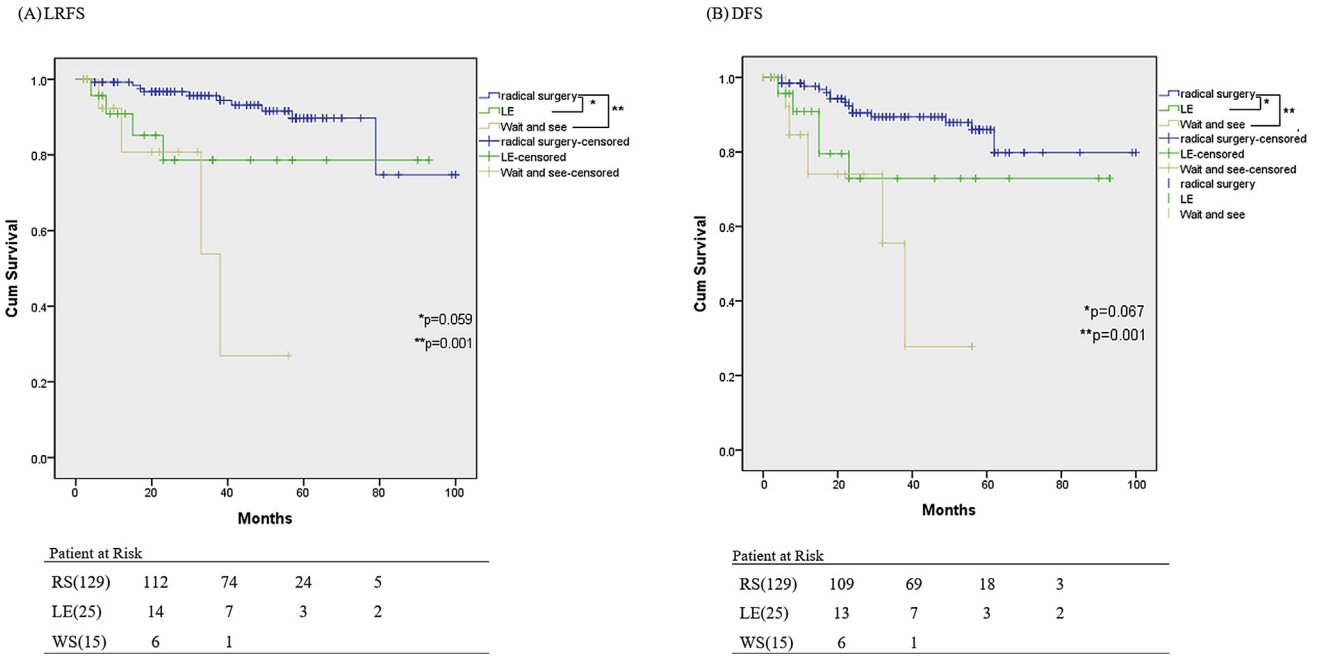

Figure 1 Local-recurrence free survival (LRFS) and Disease-free survival (DFS) of three treatments. (A) LRFS (B) DFS.

Table 4 Multivariate analysis about clinical factors for Local recurrence-free survival (LRFS).

	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (above 70)	3.451 (1.345–8.854)	0.010		
Sex	0.597 (0.230–1.548)	0.289		
Tumor height (>5 cm)	1.236 (0.464–3.296)	0.671		
Tx type		0.001		0.005
LE	3.023 (0.934–9.780)	0.065	3.252 (0.996–10.623)	0.051
WS	8.942 (2.680–29.838)	<0.001	7.163 (1.995–25.715)	0.003
cT4	11.498 (2.575–51.349)	0.001	8.206 (1.596–42.198)	0.012
cN positive	0.617 (0.378–1.009)	0.054		
Elevated CEA level (preCRT)	0.650 (0.187–2.257)	0.498		
Adjuvant CTx	0.732 (0.166–3.218)	0.680		

RS: radical surgery/LE: local excision/WS: wait and see.

Table 5 Comparison between our previous and this report.

	N. of cases	LRFS	DFS
Previous report (2006'–2011')	RS: 28	RS > LE (p = 0.039)	RS = LE (p = 0.294)
	LE: 16	RS > WS (p = 0.001)	RS > WS (p = 0.004)
	WS: 8		
This report (2008'–2017')	RS: 129	RS = LE (p = 0.059)	RS = LE (p = 0.067)
	LE: 25	RS > WS (p = 0.001)	RS > WS (p = 0.001)
	WS 15		

RS: radical surgery/LE: local excision/WS: wait and see/LRFS: local recurrence-free survival/DFS: disease-free survival.

showed similar lymph node metastasis rate (ypT0-1; 3.6%, ypT2; 18.4%). Several studies reported compromised oncologic outcome of local excision for ypT2-3, even after the salvage operation was followed.[28–31] We had 8 patients with ypT2-3 in the study (ypT2; n = 6, ypT3; n = 2), but they did not undergo completion TME according to their will. Among them, recurrence developed in 3 patients (2 local/1 distant), and all these patients received salvage operations. Unfortunately, comparing of oncologic outcome between RS and LE in ypT2-3 patients was not possible

because of small number of patients in this study. According to our study and previous evidences, ypT0-1 cancers can be treated with LE alone, but more than ypT2 cancers seems to require radical surgery.

Dattani et al[21] reviewed 17 prospective or retrospective "wait-and-see" articles. They reported a 21.6% of local regrowth rate, but low rate of 3-year distant metastasis rate and mortality (distant metastasis 6.8%, mortality 6.5%). However, they pointed out significant heterogeneity in patient selection criteria and study design of included studies. Recently, MJM van der Valk et al reported long-term outcomes of WS protocol.[20] They analyzed 1009 patients data of International Watch & Wait Database (IWWD) from 47 participating institutes (15 countries). They showed similar outcome with Dattani et al. Local regrowth (2-year) and distant metastasis (3-year) rate was 25.2% and 8%. Salvage operation was possible in 78% of patients with local regrowth, and curative R0 resection was obtained in the almost cases (99%) with 94% of 5-year disease-specific survival. In our series, similar rate of patients experienced local tumor regrowth (26.6%), but they showed poor survival outcome than other articles reported that. The reason of compromised outcome would be resulted from the high rate of omitting of salvage or palliative treatments. Based on the results of our studies as well as others, WS cannot be routinely considered for treatment of rectal cancer patients with cCR after nCRT. WS should only be considered for carefully selected patients who have will for salvage treatment.

Accurate cCR diagnosis is essential for non-operative management. In this study, we included patients who had been determined clinical CR only by MRI findings, but there are many other modalities, previously studied, including Digital rectal examination (DRE), colonoscopy, transrectal ultrasonograpy, CT, FDG-PET. However, recent studies failed to find out definite test which can accurately determine a pathologic complete response.[32–36] According to a recently published paper,[37] each of MRI, colonoscopy and transrectal ultrasonography showed only a 25% of sensitivity for CR prediction. And the combination of each 2 or all 3 methods did not improve accuracy, which is in line with other studies. In the absence of a definite CR prediction method and considering the preference of patients in non-operative treatment group, evaluating CR with MRI alone would be an advantage reflecting the actual clinical situation rather than being an important limitation of this study.

In fact, our institution has been using colonoscopy and DRE in conjunction with MRI for evaluating the post-nCRT response. A recent study has also reported that many patients had wanted to undergo non-operative treatment, even if they had been at risk of compromised oncologic outcome.[38] In line with that paper, our patients also chosen non-operative treatments, even though the results of the other tests (colonoscopy, DRE) were not consistent with MRI's results. We persuaded patients to undergo radical surgery when they were suspected to have a residual tumor in any test, even if the patient really wanted non-operative treatments.

The exact number of patients with altered treatment plans cannot be countable due to the retrospective design of this study, but it is likely that patients who were presumed to have CR in various tests simultaneously were included to the non-operative treatment groups. If more patients with a higher likelihood of CR were included in the non-operative groups, there is a possibility that local excision was overestimated which had similar outcome to the Radical surgery, in especially. Although it is impossible to compare the exact pathologic tumor stages between the Radical surgery group and the Local excision group, but statistical analysis showed no significant difference in the ypT0 ratio between two groups (Radical surgery: 35.7%; Local excision: 48.0%, $p = 0.265$). Even if more patients had been included to non-operative treatment groups who were presumed to have CR in various tests simultaneously, there is still little evidence as to whether the number of tests improves the CR predictability and therefore the survival rate. Therefore, it seems that the selection bias from CR predicting modality would not have a significant impact on the results of this study.

According to a recent review, other studies reported 22.4% (2.8–78.4%) cCR rate[21] and ours was 14.8%. WS has been performed on the assumption that patients with cCR will have similar oncologic outcomes to those with pCR; however, several studies have reported that cCR does not necessarily indicate pCR.[39–41] Our study also showed only 33.3% of pCR/cCR rate in the radical surgery group. Several studies are currently being conducted in an effort to increase "real" CR. These include studies on the development of response predictive models using molecular biomarkers, inventing sensitive biologic modifiers, modulating radiation doses or use of different chemotherapy regimens for nCRT, and adopting induction or consolidation chemotherapy with or without CRT.[42–48]

Habr-Gama's group proposed a WS protocol in which patients had a 49.2–67.1% cCR rate after nCRT, and many patients (88%) had sustained the cCR at 5 years.[49,50] However, they included cancers at relatively earlier stages and their survival outcomes could not be reproduced by other groups. They used digital rectal examination, endoluminal assessment with biopsy, CT, pelvic MRI, and/or endorectal ultrasound for cCR evaluations. And their definition of cCR was 1) absence of residual ulceration, 2) no mass or mucosal irregularity, 3) absence of extrarectal disease on imaging, 4) whitening of mucosa and telangiectasia acceptable.[51] But many institutions use diverse diagnostic modalities for cCR evaluations, and which method is effective and how to utilize them is unclear.[52]

Ideally, WS protocol for cCR rectal cancer patients after nCRT should be compared with RS in a multicenter, randomized controlled trial (RCT). However, there are several limitations to RCTs. For example, enrolling a sufficient number of patients is difficult because of the low cCR rate and lack of diagnostic consensus. Most patients with indications for RS would not want to participate in a WS protocol because of the risk of compromised survival outcomes. Furthermore, WS participants have tendency to reject salvage or palliative treatments in several previous studies. In this situation, a high-quality comparative study at a high-volume institution can be the second-best strategy.

This study presented relative clinical and oncologic outcomes according to treatment options and tried to suggest indication of each treatment option through the review of

previous reports and our results, but there are several limitations also. Because of the low CR probability, fewer enrollable patients, and short follow up periods, there are limitations in studying the outcome of Wait and see, and systemic reviews and meta-analyzes have not yielded definite conclusions due to the significant heterogeneity among studies. Although present study tried to report long-term outcomes of a relatively large single institution, the small number of patients and the relatively short follow up period are limitations also, as like previous studies. However, while most previous studies were non-comparative studies of wait-and-see itself, this study compared outcomes with other treatments which could be considered for the treatment of cCR patients. So we believe that this study will be of practical use until the RCT results are published.

5. Conclusion

The oncologic outcomes of LE was similar to those of RS with high rate of post-recurrence treatments. However, WS group showed high rate of rejection for post-recurrence treatment, and oncologic outcome was poor than RS group. WS protocol should be performed under the active surveillance program, and salvage treatment for recurrence is mandatory to secure oncologic outcomes. Applying WS protocol seems be careful until the results of RCTs are available.

Conflict of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

SSY was the main investigator, designed the study, and analyzed and interpreted the data. SYL, CHK, TKN, YJK and HRK contributed knowledge, and read and corrected the manuscript. All authors approved the final version of the manuscript.

Ethical approval

All procedures were performed following the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Review Board at the Chonnam National University Hwasun Hospital, Gwangju, South Korea approved the study (reference number CNUHH-2018-087) and was eligible for exemption of informed consent. No animal experiments were performed for this study.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.12.007.

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