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Original Article

IS THE DELAYED SURGERY AFTER NEOADJUVANT CHEMORADIATION BENEFICIAL FOR LOCALLY ADVANCED RECTAL CANCER?

Existem benefícios com a cirurgia retardada após radioterapia e quimioterapia neoadjuvante no câncer de reto localmente avançado?

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ABSTRACT – ***Background*** - Neoadjuvant treatment with radiotherapy and chemotherapy is the preferred regimen for locally advanced rectal cancer, aiming to increase resectability and decrease local recurrence. ***Aim*** - To evaluate the benefits of delayed surgery after neoadjuvant chemoradiation in advanced rectal cancer regarding aspects of tumor response, survival and its deleterious effects. ***Methods*** - Were treated 106 patients consecutively with locally advanced rectal adenocarcinoma. Neoadjuvant chemoradiation with a dose of 50.4 Gy (28 fractions), 5-fluoracil and leucovorin was given. Surgery was scheduled within five to six weeks. Patients who returned later than six weeks for the scheduled surgery were grouped into the delayed group and variables such as the downstaging rate, complete response, surgical time, blood transfusion, local recurrence, distant metastasis and survival were correlated with the remaining patients in order to determine the benefits of the delayed surgery. ***Results*** - Complete tumor response was found in 15 patients (T0=15/106 – 14.2%). Partial response was achieved in 38 patients (34.9%), while one patient had pT0N2 staging. The mean follow-up was 35.6 weeks for the six weeks group, and 32.2 weeks for the delayed group. There were no significant differences between the two groups in terms of downstaging, complete tumor response, surgical time, blood transfusion and early post-operative complications. Although delayed surgery didn't have a significant difference regarding the local recurrence (p=0.1468), it showed a strong tendency in the delayed group of having a lower risk of distant metastasis (p=0.0520). ***Conclusion*** - Delayed surgery after chemoradiation offered no clear benefits in terms of complete tumor response or downstaging. Predictive molecular factors should be investigated in the future for the proper selection of patients who will benefit from chemoradiation.

HEADINGS - Radiotherapy. Drug therapy. Rectal neoplasms.

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RESUMO - **Racional** - Tratamento neoadjuvante com radioterapia e quimioterapia é o esquema preferencial para câncer de reto localmente avançado, tendo por objetivo aumentar a ressecabilidade e diminuir a recidiva local. ***Objetivo*** - Avaliar os benefícios da operação tardia após radioterapia e quimioterapia neoadjuvante em câncer de reto localmente avançado quanto à resposta da regressão tumoral, sobrevida e efeitos adversos. ***Métodos*** - Foram tratados consecutivamente 106 pacientes, portadores de adenocarcinoma do reto localmente avançado no período pré-operatório com radioterapia na dose de 50,4 Gy (28 frações) e quimioterapia com 5-fluoracil e leucovorin. A operação foi programada entre cinco e seis semanas. Pacientes que retornaram após seis semanas por motivos diversos foram agrupados em grupo de operação tardia. Variáveis como diminuição do estádio, remissão tumoral completa, tempo cirúrgico, transfusão sanguínea, recidiva local, metástase e sobrevida foram correlacionadas com o restante dos pacientes a fim de verificar os seus benefícios. ***Resultados*** - Remissão completa do tumor foi encontrada em 15 pacientes (T0=15/106 – 14,2%). Resposta parcial em 38 (34,9%); entretanto em um paciente a resposta foi pT0N2. O seguimento médio foi 35,6 semanas e 32,2 semanas para grupo de operação em seis semanas e grupo de cirurgia tardia. Não houve diferença entre os dois grupos quanto à diminuição de estádio, remissão tumoral completa, tempo cirúrgico, transfusão sanguínea e complicações cirúrgicas precoces. Embora a operação tardia não apresentasse diferença significante quanto à recidiva local (p=0,1468), ela mostrou tendência em menor risco de metástase à distância (p=0,0520). ***Conclusão*** - Operação tardia após tratamento neoadjuvante não oferece benefícios evidentes em termos de remissão completa ou diminuição do estádio tumoral. Fatores moleculares preditivos devem ser investigados no futuro para melhor seleção de doentes que poderão beneficiar-se com o tratamento neoadjuvante.

DESCRITORES - Radioterapia. Quimioterapia. Neoplasias retais.

INTRODUCTION

Neoadjuvant chemoradiation (CRT) followed by surgery is the standard of care for locally advanced rectal cancer in order to increase the resectability and decrease the local recurrences. Downstaging and even complete remission after chemoradiation have been reported. The remission rate ranged between 9 to 30%[2,3,19,23,25,26] but it did reach as high as 48% in some studies[12]. Due to high rate of complete tumor response, some researchers have adopted the policy of the watch and wait[10,11], but there are still challenges in finding predicting factors on tumor response. The complete response of tumor or downstaging after CRT could be beneficial in the recurrence rate and survival. There are many researches showing that delayed surgery can increase the downstaging or even the complete tumor response[1,15]; nevertheless, it can produce pelvic tissue fibrosis which in terms would increase surgical difficulty and morbidity.

The aim of this study was to correlate the delayed surgery to the tumor response, survival and its potential deleterious effects after chemoradiation in advanced rectal cancer.

METHODS

From March 2004 to March 2010, were treated 225 consecutive patients diagnosed with rectal adenocarcinoma in the School of Medicine and Central Hospital of Santa Casa of São Paulo, São Paulo, SP, Brazil, of which 106 patients had locally advanced mid and low rectal cancer. Neoadjuvant chemoradiation was followed by tumor resection; procedures such as abdominoperineal resection (APR) or low anterior resection (LAR), and coloanal anastomosis were performed according to the distance of the tumor from the anal verge. A radiation dose of 5040 cGy was applied in 28 fractions during the period of five and a half weeks. Was given 5-fluoracil and folinic acid during the first and fifth week of the radiation. After the neoadjuvant chemoradiation, the surgery was scheduled within five to six weeks.

The patients were submitted to preoperative staging by using magnetic nuclear image (MRI) in order to identify the locally advanced rectal cancer. The selection criteria were the following: 1) patients with tumor in stage T3 or T4 or any lymph nodes (N1 or N2 with any T) seen in MRI; 2) tumors located on the middle or distal rectum, reachable by digital examination and preoperative diagnosis of adenocarcinoma confirmed by biopsy. The criteria for exclusion were: 1) unresectable distant metastasis such as liver or lung nodules that was unsuitable for the surgical treatment and poor clinical conditions; 2) obstruction or rectovaginal fistulas.

The pathologic findings were compared with preoperative MRI staging and three categories of radiation effects were recorded: 1) complete tumor response when there was no residual tumor on the specimens (T0 any N); 2) downstaging to a lower staging and 3) no tumor response when the same staging or higher staging was found in the pathologic studies of the specimens.

Abdominoperineal resection (APR) or low anterior resection (LAR) with total mesorectum excision (TME) and defunctional ileostomy was performed and postoperative adjuvant chemotherapy was initiated on the 30th day.

Patients who returned later than six weeks for the scheduled surgery were grouped into the delayed group and variables such as the downstaging rate, complete response, surgical time, blood transfusion, local recurrence, distant metastasis and survival were correlated with the remaining patients in order to determine the benefits of the delayed surgery.

Statistical analysis

Data were summarized by frequencies and percentages. Chi-square and Fisher's exact tests were performed. Student's T test was used for comparing blood transfusion and length of surgical time. Survival rates were estimated by the Kaplan-Meier method and compared with the log-rank test. Patients without events were censored at the time of the last follow-up. Statistical analysis was performed using Medcalc version 11.5.1.0 (Medcalc software BVBA).

RESULTS

A total of 106 patients treated consecutively from March 2004 to March 2010 were selected for neoadjuvant chemoradiation. The tumors were located at the middle third of rectum (above 5 cm from anal verge) in 38 cases and distal in 68 (5 cm and below from anal verge). Preoperative staging with MRI revealed T2=8 (N+), T3=82, T4=16 (Table 1). Complete tumor response was found in 15 patients (T0=15/106 – 14.2%). Downstaging was achieved in 53 patients (53/106 - 50%). The MRI preoperative staging showed lower grade of staging than the pathologic finding in T grading in six cases (5,7%) and in lymph nodes metastasis in 22 cases (20,6%). The average time interval between CRT and surgery for patients who presented T up staging was six weeks and N up staging was 8.9 weeks, while the counterpart remaining was 9.5 weeks.

TABLE 1 - Pre-neoadjuvant and postoperative pathologic staging

	Pre-neoadjuvant			Postoperative		
	N0	N1	N2	N0	N1	N2
T0				14	0	1
T1				6		1
T2		8		22	1	
T3	45	37		29	16	12
T4	11	5		2	1	
	56	50		73	18	14

Low anterior resection was performed in 43 cases and in 25 cases a defunctioning ileostomy was performed. Abdominoperineal resection was done in 61 cases. The mean follow-up was 32.2 weeks.

All the patients were scheduled for surgery within five or six weeks. Although they were scheduled to return at this time interval, 74 returned within a period longer than six weeks with an average of 11 weeks (7-27 weeks).

The mean follow-up in the delayed group was 32.2 (10-78) weeks and 35.6 (10-93) weeks for the six weeks group.

There were fifteen patients who achieved a complete tumor response (14.2%) after neoadjuvant CRT, but one patient had a lymph node metastasis (T0N2); consequently, the complete tumor response rate was 13.2% (T0N0). Partial response was observed in 37 patients (34.9% -Table 2).

TABLE 2 - The influence of delayed surgery on tumor response after neoadjuvant chemoradiation, comparing the interval of five to six weeks with more than six weeks

	Five to six weeks	More than six weeks	Total
Complete response (CR)	6 (18,8%)	9 (12,2%)*	15(14,2%)
Downstaging (DS)	8 (25,0%)	29(38,7%)	37(34,9%)
CR + DS	14 (43,8%)	38 (50,7%)**	52(49,1%)
No effect	18	36	54
Total	32	74	106

*p=0,3717 **p=0,4723 $\chi 2$ test

Delayed surgery produced no increased complete tumor response. Patients who had five to six weeks between CRT and surgery had the same rates of complete response and dowstaging, compared with those who had a longer interval of time. Complete response was achieved in six (18.8%) in the six weeks group and nine (12.2%) in the delayed group (p=0.3717). Respectively, the downstaging rate was 25% and 38.7% (p=0.4823) (Table 2).

Delayed surgery also caused no major surgical difficulties. The surgical time, blood transfusion and early postoperative complications were similar. (Table 3). The difference between the recurrence rate for the six weeks group and the delayed group was not statistically significant, 1(3.1%) and eight (10.8% p=0.1468), respectively. Furthermore, there was a lower rate of distant metastasis in the delayed group when compared to the six weeks group, 10 (31.25%) and 11 (14.9%), respectively. Although not significant, but a strong trend for a lower risk of distant metastasis (p=0.0520) was observed.

The tumor response and downstaging showed an impact on the survival rate. Patients who had complete response and partial response had a higher survival probability (Kaplan-Meier Survival Curve, Logrank test, CR x DS x NR p=0.0487). There was a slightly higher survival probability in the delayed group, although it was not significant (p=0.1940). The CEA blood level did not show difference in terms of downstaging or complete tumor response (CEA >10 ng/ml and CEA<10 ng/ml, 28.3% and 51.6%, respectively, p=0.2554). Higher level of CEA was not associated to the higher rate of local recurrence (p=0.2799), but there was a higher rate of distant metastasis when CEA level was higher than 10 ng/ml (Table 4). The survival probability curve was better in patients who had a CEA level below 10 ng/ml (26 x 35weeks, p=0.0098).

TABLE 3 - The influence of delayed surgery on tumor response after neoadjuvant chemoradiation on the local recurrence rate, metastasis, transfusion, operating time and early postoperative complications, comparing the interval of five to six weeks with more than six weeks

	Five to six weeks	More than six weeks	Total	p
Local Recurrence	1(3,1%)	8(10,8%)	9	0,1468
Distant metastasis	10(31,25%)	11(14,9%)	37	0,0520
Blood transfusion (unit)	2,9	1,9		0,0856
Operating time (min)	279	278		0,9385
Early complication	15(46,8%)	45(60,8%)	54	0,1838
Total	32	74	106	

TABLE 4 - Blood CEA level and rate of local recurrence, distant metastasis, downstaging, complete tumor response and survival

	CEA>10	CEA < 10	p	Total
Local recurrence	4	4	0,1799	8
Distant metastasis	11	9	0,0262	37
Downstaging	13 (28,3%)	33 (51,6%)	0,2554	46
Complete response	5	9	0,8850	14
Survival (weeks)	26		0,0098	
Total	33	64		97

The tumor response and downstaging were associated to the lower rate of local recurrence and distant metastasis (Table 5). None of the 14 patients who presented complete tumor response had local recurrence or distant metastasis (p=0.0331).

TABLE 5 - Relationship between the tumor response and local recurrence and distant metastasis

	Complete response	Downstaging	No effect
Metastasis	0	7*	13**
Local recurrence	0	4*	5*
Total	14	39	53

* NS **P=0,0331

DISCUSSION

Neoadjuvant preoperative chemoradiation is nowadays the standard care in patients with locally advanced rectal cancer. The purpose is to decrease local recurrence and to achieve a higher resection rate. Many researchers have been very enthusiastic about reports of complete tumor response rate between 9% to 30%[2,3,19,23,25,26]. Longer interval of time between CRT and surgery has been suggested in order to achieve better tumor response[10,11,12].

Endorectal ultrasound and MRI have been used for the selection of patients for this combined treatment. Was used here MRI as a standard clinical staging to select patients for preoperative CRT. Was found that higher tumor grade (T) staging in six (5.7%) and N staging in 22 (20.6%). There are two possible causes for this: first, there was under staging by MRI and second, the delay to surgery could allow the continuation of tumor growth. Guillem et al.[9] have shown a 22% undetected mesorectum nodal involvement in pathologic study. An over staging and consequently over treatment had occurred in 18% and the estimated under staging rate could be even higher. In present study, was found 30.2% of lymph node involvement in the pathologic specimens. There was 20.6% of up staging (higher pN than the cN staging), meaning that the rate of under staged lymph node involvement should be higher than this.

Suppiah et al.[20] have shown an accuracy of MRI-staging as poor as 43% (21/49) with over and under staging in 43% (21/49) and 14% (7/49), respectively. T-stage accuracy was 45% (22/49) with over-staging in 33% (16/49) and under staging in 22% (11/49). A high negative predictive value (NPV) of 93% and a positive predictive value (PPV) of 43% were observed. Over-staging is due to poor PPV; conversely, this series had 20% of higher N stage and 5.7% T stage, with lower NPV than that found by the others. Consequently, was not perform MRI assessment after CRT, because of the poor accuracy of high over and under staging reported by the studies[9,14,17,20], as well as for not adopting the "wait and watch policy". Was performed surgery in all the patients with the exception of those who refused the procedure.

Other staging image such as endorectal ultrasound is even less accurate in terms of the nodal assessment[9].

One patient had complete tumor response (pT0), but lymph nodes metastasis was present (pT0N2). This is another argument against the "wait and watch" policy. The preoperative MRI is often disappointing, occurring under staging, particularly with respect to the lymph nodes that could be as high as 20% as seen in these data. A lymph node located at a higher level of mesorectum could be misdiagnosed and not receive radiation because of the restricted field.

To optimize the response and decrease toxicity, a period of six weeks between CRT and surgery is recommended[6]. Employing a 41Gy dose, a time interval as short as five days was undertaken by Couke et al.[4]. Kurt et al.[16], used a 50.4Gy dose preoperative CRT and performed surgery with a mean delay of 15 days. The main concern about the delayed surgery is surgical difficulty due to tissue fibrosis. Francois et al.[6] showed the benefit of downstaging, sphincter saving without an increase in complications by delaying the time interval from two to three and six to eight weeks. Since then, the interval of six weeks was followed by many reports. Campos-Lobato et al.[1] have shown that patients undergoing surgery ≥ eight weeks after chemoradiation, experienced a significant improvement in pathologic complete response rate (30.8% vs. 16.5%) Recently, some researchers have adopted an interval of more than eight weeks[10,11]. A time interval of as long as 12 weeks, or even the "wait and watch" policy have been adopted and achieved as high as 48% of clinical remission[12]. However, there is a difference between clinical complete response and pathologic complete response. Thus, it should be expected a lower pathologic response than the clinical response. Others reported not so encouraging results, similar to the results by Garcia et al.[7]. Here was also found only a modest improvement on downstaging and no increase of the complete tumor response rate by delaying the surgery after CRT. Despite having had no more difficulties, surgical complications and rate of transfusions, is not seen advantage in prolonging the waiting time after CRT.

There were concerns about postoperative complications followed by neoadjuvant chemoradiation, but recent reports have shown safety in extending the time interval for surgery[22,24]. Recently, it has been reported that the delayed surgery did not increase complications although it results in only a modest increase in pCR rate in patients undergoing TME for locally advanced rectal cancer[7].

Predictive factors for downstaging have been investigated and it could be an important advance in selecting properly the patients for CRT. Excluding patients who are not benefited from this combined therapy, the toxicity of CRT and complications could be avoided. Moureau-Zabotto et al.[18] showed that the CEA level below 5 ng/ml and the small tumor size were associated to tumor downstaging. Was not found any improvement in this series. Blood level of CEA below 10 ng/ml did not show any improvement on downstaging. Was tested CEA level > 5 as the research cited anteriorly; in addition, was not observed any advantage in downstaging or tumor response. Was found only poor survival curve and distant metastasis in patients with high level of CEA.

Was also found an improved survival curve in patients presenting tumor response, downstaging and complete response after CRT. Other reports had found an improved progression-free survival and an overall survival of locally advanced rectal adenocarcinoma[5,18,21]. The tumor response and downstaging were not attributed to delayed surgery and it did not contribute to a better survival curve. Despite not having had more difficulties, surgical complications and rate of transfusions, was seen no advantage in prolonging the waiting time after CRT.

Recent reports related to predicting factors for tumor response have been made. Grimminger et al.[8], suggested that pretreatment intratumoral EGFR and VEGF mRNA expression levels as well as K-Ras mutation status are predictive markers of pathologic response

to neoadjuvant cetuximab-based chemoradiation in locally advanced rectal cancer. However, Kim et al.13, have shown that VEGF as other molecular markers (cyclooxygenase-2, epidermal growth factor receptor, Ki-67, p21, and thymidylate synthase) did not predict tumor response. Only the marker survivin has shown as a predicting factor for poor tumor response. Yan et al.27, have shown that SMAC expression (second mitochondria-derived activator of caspase) as a predicting factor for good outcome. Predictors or predictive molecular markers are yet to be found to select patients who will have complete or nearly complete tumor response to the CRT.

CONCLUSION

Delayed surgery after CRT offered no clear benefits in terms of complete tumor response or downstaging.

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