



## Original Research Article

## Time to surgery and pathologic complete response after neoadjuvant chemoradiation in rectal cancer: A population study on 2094 patients



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## ABSTRACT

**Background:** To retrospectively evaluate the difference in terms of pathologic complete response (pCR) according to time elapsed between chemoradiation (CRT) and total mesorectal excision (TME) on a large unselected real-life dataset of locally advanced rectal cancer (LARC) patients.

**Methods:** A multicentre retrospective cohort study of LARC patients from 21 Italian Radiotherapy Institutions was performed. Patients were stratified into 3 different time intervals from CRT. The 1st group included 300 patients who underwent TME within 6 weeks, the 2nd 1598 patients (TME within 7–12 weeks) and the 3rd 196 patients (TME within 13 or more weeks after CRT), respectively.

**Results:** Data on 2094 LARC patients treated between 1997 and 2016 were considered suitable for analysis. Overall, 578 patients had stage II while 1516 had stage III histological proven invasive rectal adenocarcinoma. A CRT schedule of one agent ( $N = 1585$ ) or 2-drugs ( $N = 509$ ) was administered. Overall, pCR was 22.3% ( $N = 468$  patients). The proportion of patients achieving pCR with respect to time interval was, as follows: 12.6% (1st group), 23% (2nd group) and 31.1% (3rd group) ( $p < 0.001$ ), respectively. The pCR relative risk comparison of 2nd to 1st group was 1.8, while 3rd to 2nd group was 1.3. Moreover, between the 3rd and 1st group, a pCR relative risk of 2.4 ( $p < 0.01$ ) was noted. At univariate analysis, clinical stage III ( $p < 0.001$ ), radiotherapy dose  $>5040$  cGy ( $p = 0.002$ ) and longer interval ( $p < 0.001$ ) were significantly

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correlated to pCR. The positive impact of interval ( $p < 0.001$ ) was confirmed at multivariate analysis as the only correlated factor.

**Conclusion:** We confirmed on a population-level that lengthening the interval (>13 weeks) from CRT to surgery improves the pathological response (pCR and pathologic partial response; pPR) in comparison to historic data. Furthermore, radiotherapy dose >5040 cGy and two drugs chemotherapy correlated with pPR rate.

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## Introduction

The current standard neoadjuvant treatment for locally advanced rectal cancer (LARC) is either the use of preoperative short-course radiotherapy (RT) or conventionally fractionated RT with continuous 5-FU infusion or oral capecitabine (chemoradiation or CRT), followed by total mesorectal excision (TME) surgery 6–8 weeks later. CRT is associated with improved local control (LC) rate, tolerable toxicity profile and high compliance rate, and tumor downsizing with a potentially increased sphincter preservation rate in patients with low-lying tumors [1,2].

Although response to CRT is variable, it has been recognized that LARC patients achieving a pathological complete response (pCR) have a better prognosis compared to non-responders. In fact, several series and meta-analyses have shown a clear correlation between the pCR and clinical outcomes in terms of LC, metastases free survival, disease free survival and overall survival [3–8]. Conversely, other two meta-analyses failed to show an improved outcome in patients with pCR [9–10].

In series of LARC patients treated with radiotherapy (RT) or 5-fluorouracil based-CRT, the pCR rates ranged from 11.4% to 15% [11–13]. This rate can be improved given the versatility of preoperative long course CRT, allowing drug and RT dose intensification as well as time interval (CRT-surgery) modulation.

Second generation phase II trials combining oxaliplatin or raltitrexed to neoadjuvant 5-FU/capecitabine-CRT suggested higher pCR rates range (11–42%) in comparison with preoperative 5-FU-CRT alone [14]. Subsequently, four randomized phase III trials (ACCORD 12, STAR-01, NSABP-R04 and PETACC-6) did not confirm a significant improvement of the pCR rate range (14–19.2%) with the addition of oxaliplatin to preoperative 5-FU-based CRT [15–18]. On the contrary, the recent phase III trial CAO/ARO/AIO-04 showed that addition of oxaliplatin to 5-FU-based CRT improved pCR rate and disease free-survival compared to 5-FU-CRT alone (13% versus 17%) [19]. Moreover treatment intensification was pursued through the RT dose escalation. A systematic review and meta-analysis on dose escalation showed an association between pCR and higher boost doses [20], while a model on dose-response relationship confirmed the correlation between total delivered dose and possibility to achieve pCR [21].

Finally, the so-called time factor, as a potential factor in pCR rate improvement, is a debated subject in literature. The Lyon R90-01 trial, published in 1999, was the first randomized trial evaluating the CRT-surgery time interval [22]. Two-hundred and ten LARC patients were randomized to surgery either after a short (less than 2 weeks) or long (6–8 weeks) interval from RT (total dose = 39 Gy/3 Gy per fraction). The longer interval was associated with a significantly higher proportion of patients with ypT0–1 disease but not pCR. This 6–8 weeks interval has become routine practice after CRT for rectal cancer. Subsequently, it was observed that waiting longer than 6 weeks after CRT is associated with an increased pCR and near pCR rates. This led to further retrospective analyses on the association between interval length and pCR rate. In these retrospective studies an interval beyond 10 weeks after

CRT was found as an independent factor in improving pCR rate (between 18% and 24%), and disease-free survival [23–25].

Indeed, complete tumor regression may take months, as shown by a growing body of evidences [26–28]. In the past, the concern about delayed surgery beyond 6–8 weeks was due to theoretically increased risk of complications, more technical difficulty due to fibrosis, and risk of loco-regional progression of residual disease. To date, these issues are largely overcome by literature findings demonstrating similar morbidity regardless of waiting time [23–25,29,30].

A further emerging issue about lengthening the interval before surgery is that it permits administration of chemotherapy during the break. In the recent study of Garcia-Aguilar and colleagues [31], there was a statistically significant difference between the group which underwent surgery after 6–8 weeks without adjuvant chemotherapy (18% pCR) and the group receiving 6 cycles of chemotherapy (FOLFOX 6) in the pre-surgical interval (38% pCR). This result seems to suggest that not only the break improves the oncologic outcome, but also chemotherapy administered in this interval might contribute.

Based on the hypothesis that a considerable increase of time to surgery might itself justify the higher response rates, a proposal was presented by the Gastro-Intestinal Working Group of the Italian Association of Radiation Oncology (AIRO-GI) to Italian centers treating LARC patients preoperatively, to combine their retrospective series. The aim was to perform a population based analysis to evaluate the difference in terms of pathologic response according to time of surgery on a large LARC population of patients treated with modern CRT techniques and TME.

## Patients and methods

### Study design and participants

We performed a multicenter retrospective cohort study on LARC patients treated in 21 Italian Radiotherapy Institutions. Patients' data were obtained from the historical database of gastrointestinal radiation oncologists who joined the study. Patients must have signed informed consent to the use of their clinical data for scientific purposes. Inclusion criteria were: age  $\geq 18$  years, clinical stage II (T3–4, N0) or III (any T, N1–2) invasive rectal adenocarcinoma, distal tumor border within 12 cm from the anal verge by proctoscopy. Local staging was performed by endorectal ultrasound or phased-array MRI. Before treatment, patients underwent a full colonoscopy, abdomino-pelvic CT scan and chest radiograph/CT. Patients were required to have an ECOG performance status score of 0/1 or a comparable Karnofsky score.

### Procedures

The AIRO-GI asked participating centers for minimal data sets including: gender, age, clinical stage, type of treatment and pathological response. No information about workup staging procedures or acute and late toxicity was recorded, as well as about quality of surgical procedures or subsequent outcomes. Chemotherapy schedule and radiotherapy dose were according to the treating

investigator's choice. However, non metastatic patients included into the analysis had to be treated by long course CRT with one or two drugs during the last 20 years. 3D-conformal or intensity-modulated radiation treatment was required in the inclusion criteria. Surgery was performed according to the principles of TME. In the absence of standardized criteria to analyze the surgical specimen, local practice was accepted, and no attempt was made to review pathologic findings centrally. Patients were stratified into 3 different time intervals and none received chemotherapy between CRT and surgery. The 1st group included patients who underwent TME within 6 weeks, the 2nd within 7–12 weeks and the 3rd within 13 or more weeks after CRT.

### Outcomes

The primary endpoint of the study was to evaluate the proportion of patients achieving a pCR (defined as the absence of tumor cells in the surgical specimen, both at the primary tumor site and at regional lymph nodes) in each study group. Secondary endpoint was to evaluate the proportion of patients having any downstaging which was defined as ypStage 0-I (ypT0-2N0M0) [32]. These rates were correlated with time interval between CRT and TME.

### Statistical analysis

Data were centrally collected at the Fondazione “Giovanni Paolo II”-UCSC, Campobasso and entered into an electronic database. The data processing in collaboration with the Department of Radiotherapy KBO Labs at Università Cattolica S. Cuore of Rome occurred in the last six months of 2016. Heterogeneity among study groups were evaluated by Mann–Whitney and Pearson's chi squared test. The three different groups were compared using relative risks (RR) measure and test. A RR greater than 1 indicates a positive association with the occurrence of pCR; a RR less than 1 a negative association with the occurrence of pCR. A  $p$  value  $<0.05$  was considered statistically significant. A linear correlation was used to calculate the rate of pCR per each waiting week. An univariate and multivariate logistic regression were used to model the pCR probability using clinically relevant variables. Variables considered in multivariable analyses were selected by significance during univariable analysis. The same analysis was performed for pathological partial

response (pPR). Statistical analysis was performed using R version 3.3.1 [33].

### Results

Between February 1997 and March 2016, 2358 patients from the historical database of AIRO GI oncologists joining the study were centrally collected. Of these, 68 patients were excluded from the final analysis for clinical stage and 196 patients for no per-protocol treatment (short course radiotherapy,  $N=90$ , or no chemotherapy,  $N=106$ ).

Therefore, data on 2094 LARC patients were considered suitable for analysis. The Institutions pooling data were distributed in 5 major Italian areas (North East: 14%, North West: 24%, Central North: 24%, Central South: 33%, South and Islands: 5%), identifying a predominance of the Northern part (62%) reflecting the distribution of radiotherapy Centers throughout the Country.

Temporal span of recruitment and type of treatment are summarized in Table 1.

As reported in Procedures, patients were stratified into 3 different groups based on time intervals from CRT. The 1st group included 300 patients who underwent TME within 6 weeks, the 2nd 1598 patients (TME within 7–12 weeks) and the 3rd 196 patients (TME within 13 or more weeks after CRT), respectively.

Table 2 lists patients' demographics and tumor characteristics in the whole series and into the 3 different groups stratified according to time interval. Age and staging heterogeneity among the study groups was detected by Mann–Whitney and Pearson's chi-square test, respectively.

Overall, pCR rate was 22.3% ( $N=468$  patients). Considering time as a continuous variable, median time from CRT end to surgery for the entire population was 9 weeks (range: 1–52 weeks). By splitting the population according to median time to surgery, 1332 patients underwent surgery before 9 weeks, while 762 later. The delayed surgery group showed a better pCR rate (19.6% versus 27.0%,  $p < 0.001$ ).

Moreover, dividing the 2094 assessable patients according the aforementioned time intervals, the proportion of patients achieving pCR increased with time interval as follows: 12.6% (1st group), 23% (2nd group) and 31.1% (3rd group) ( $p < 0.001$ ), respectively

**Table 1**  
Temporal span of recruitment and type of treatment.

Gender		N° (%)	
Recruitment period (years)	Male	1328 (63)	
	Female	766 (37)	
Concomitant Chemotherapy schedule	1997–2002	148 (7)	
	2003–2008	515 (24.6)	
	2009–2016	1431 (68.4)	
Radiotherapy median dose, range (cGy)	One-drug	1585 (75.7)	
		Capecitabine	1044 (65.8)
	Two-drugs	5-FU	519 (32.7)
		TT*	21 (1.3)
		Oxaliplatin	1 (0.06)
		5-FU + Oxaliplatin	509 (24.3)
		Capecitabine + Oxaliplatin	201 (39.5)
		Raltitrexed + Oxaliplatin	192 (37.8)
		Capecitabine + TT	70 (13.8)
		5-FU + Mitomicin-C	28 (5.5)
5-FU + TT	11 (2.1)		
Patients irradiated with $\leq 5040$ cGy		7 (1.3)	
	Patients irradiated with $>5040$ cGy	5040 (2660–6000)	
		1560 (74.5)	
		534 (25.5)	

\* TT = target therapy (Panitumumab, Cetuximab, Bevacizumab, Gefitinib).

**Table 2**  
Patient and tumor characteristics.

	All (N = 2094)	Group 1: TME within 6 weeks (N = 300)	Group 2: TME between 7–12 weeks (N = 1598)	Group 3: TME ≥13 weeks (N = 196)	P value	
Age, median (range)	65 (23–89)	64 (23–88)	65 (25–89)	67 (32–83)	<0.01 <sup>a</sup>	
Gender, N (%)	Male	1328 (63%)	179 (60%)	1025 (64%)	124 (62%)	0.29 <sup>b</sup>
	Female	766 (37%)	121 (40%)	573 (36%)	72 (36%)	
T stage, N (%)	T2	95 (5%)	13 (4%)	71 (4%)	11 (5%)	<0.01 <sup>b</sup>
	T3	1747 (83%)	220 (73%)	1369 (85%)	158 (80%)	
	T4	252 (12%)	67 (22)	158 (9%)	27 (13%)	
N stage, N (%)	N0	578 (28%)	110 (36%)	415 (25%)	53 (27%)	<0.01 <sup>b</sup>
	N1	1122 (53%)	133 (44%)	874 (54%)	115 (58%)	
	N2	394 (19%)	57 (19%)	309 (19%)	28 (14%)	
Clinical stage, N (%)	II	578 (28%)	110 (36%)	415 (25%)	53 (27%)	<0.01 <sup>b</sup>
	III	1516 (72%)	190 (63%)	1183 (74%)	143 (72%)	

Descriptive analysis of whole study population. *p* value tests the heterogeneity between study groups.

<sup>a</sup> Mann-Whitney test.

<sup>b</sup> Pearson's Chi square test.

**Table 3**  
Pathological tumor response.

	All (N = 2094)	Group 1: TME within 6 weeks (N = 300)	Group 2: TME between 7 and 12 weeks (N = 1598)	Group 3: TME ≥13 weeks (N = 196)	P value
pCR, N (%)	468 (22.3%)	38 (12.6%)	369 (23%)	61 (31.1%)	<i>p</i> < 0.01
pPR, N (%)	1139 (54.4%)	140 (46.6%)	877(54.8%)	122 (62.2%)	<i>p</i> < 0.01

Data are pCR and pPR events number (%). *p* value tests the null hypothesis of equal proportions across study groups (Pearson's Chi square test).

(Table 3). The 2nd group had a pCR relative risk of 1.8 compared to 1st group, while the 3rd group had a pCR relative risk of 1.3 if compared to 2nd group. Moreover, the 3rd group had a pCR relative risk of 2.4 compared to 1st group (*p* < 0.01).

A linear correlation showed that the rate of pCR improvement was 1.5% per week of waiting (about 0.2%/die). Cumulative pCR rate progressively increased until 22th week, thereafter reaching a plateau. The rate of pCR was 16% in the first 56 years, 22% in the second 6 and 22% in the last 8 years under analysis.

At univariate analysis, clinical stage III (*p* < 0.001), radiotherapy dose >5040 cGy (*p* = 0.002) and longer interval (*p* < 0.001) were significantly correlated to pCR. The positive impact of interval (*p* < 0.001) was confirmed at multivariate analysis, remaining the only correlated factor (Table 4).

Concerning the secondary endpoint, pPR were recorded in 1139 (54.4%) patients. Splitting population according to median time to surgery (9 weeks), the delayed surgery group showed a better pPR rate (58.5% versus 52.0%, *p* = 0.004).

**Table 4**  
Univariate and multivariate analyses for pathologic complete response (pCR) and pathological partial response (pPR) according to patient and treatment variables.

Variable	pCR		pPR	
	Univariate <i>p</i> value <sup>a</sup>	Multivariate <i>p</i> value <sup>b</sup>	Univariate <i>p</i> value <sup>a</sup>	Multivariate <i>p</i> value <sup>b</sup>
Gender	ns	–	ns	–
Stage				
II	<b><i>p</i> &lt; 0.001</b>	ns	<b><i>p</i> &lt; 0.001</b>	<b><i>p</i> &lt; 0.001</b>
III*				
Dose*	<b><i>p</i> = 0.002</b>	ns	<b><i>p</i> = 0.01</b>	<b><i>p</i> = 0.006</b>
Chemotherapy schedule				
1 drug	ns	–	<b><i>p</i> = 0.04</b>	<b><i>p</i> = 0.01</b>
2-drug*				
Time interval*	<b><i>p</i> &lt; 0.001</b>	<b><i>p</i> &lt; 0.001</b>	<b><i>p</i> &lt; 0.001</b>	<b><i>p</i> = 0.001</b>

<sup>a</sup> Significant *p* values (*p* value ≤ 0.05) are in bold.

<sup>b</sup> Only variables with a *p* value ≤ 0.05 in the univariate logistic regression analysis were included in the multivariate model.

\* stage III, higher dose, 2-drug schedule and longer interval correlated with better pathological response. Dose and time interval were considered as continuous variables in the logistic regression analysis.

On the other hand, from the 2094 assessable patients according to the aforementioned time intervals, the proportion of patients achieving a pPR increased with time interval as follows: 46.6% (1st group), 54.8% (2nd group), and 62.2% (3rd group), respectively (Table 3). The 2nd group had a pPR relative risk of 1.7 compared to 1st group, while the 3rd group had a pPR relative risk of 1.1 if compared to 2nd group. Moreover, the 3rd group had a pPR relative risk of 1.3 compared to 1st group (*p* < 0.01).

At univariate and multivariate analyses, clinical stage III, radiotherapy dose >5040 cGy, two drugs chemotherapy, and longer interval were significantly correlated to pPR (Table 4).

## Discussion

A retrospective population study was performed by 21 Italian radiotherapy Institutions with the aim to evaluate the impact of lengthening the time after preoperative CRT without interval chemotherapy on pathological response.



Throughout the last 20 years, the pCR rate gradually increased from 16% in the first six years to 22% thereafter. The median interval time before surgery was 9 weeks in the overall series with a significant advantage in term of pCR and pPR for late surgery. Moreover, the pCR rate significantly increased according to selected time interval ranging from 12.6% for patients who underwent TME within 6 weeks to 23% and 31.1% for those who received surgery within 7–12 weeks and  $\geq 13$  weeks after CRT, respectively, with the 3rd group having a pCR relative risk of 2.4 compared to 1st group ( $p < 0.01$ ). The higher response rate correlation with prolonged interval was confirmed at multivariate analysis. Similar results were recorded concerning pPR.

In the past 20 years, the increased awareness about the importance of pCR in LARC patients led to pursuing this goal by (i) increase of total RT dose and use of altered fractionations, (ii) new chemotherapy schedules, (iii) lengthening the time interval before surgery, with the aim to improve the proportion of patients for which organ-preserving strategies might be possible, either by local excision [34] or a “wait-and-scan” strategy [35].

A systematic review and meta-analysis on 18 studies (1106 patients) associated the pCR-rate with doses higher than 60 Gy [20]. A recent mathematical prediction model on pCR-rate showed that response exponentially increases with a dose of 60 Gy and that 50% of patients could reach pCR with 92 Gy [21]. In our study, pCR-rate was correlated with higher doses at univariate analysis, but this correlation was lost at multivariate analysis perhaps due to the greater weight of the time factor or because of groups heterogeneity and relatively paucity of pCR cases. In fact, in pPR analysis, where number of cases was higher, radiotherapy dose  $>5040$  cGy, maintained a significant correlation also at multivariate analysis, as well as two drugs chemotherapy and prolonged time interval.

Combining 5-FU/capecitabine-based neoadjuvant chemoradiotherapy with oxaliplatin, or targeted therapies, as bevacizumab and cetuximab, has been tested in clinical phase I-III trials. However, the use of concurrent combination chemotherapy or targeted agents outside clinical trials is currently not recommended [36].

Time to surgery was identified as a factor influencing tumor response with a higher downstaging after the 7–8 week after CRT by several authors [10,22–24,28]. In recent years there was a trend to delay surgery until the 15th or 16th week after CRT start (10–11 weeks from the end of CRT) due to the higher chances of pCR [25]. We have to consider that specific reasons can drive to surgical resection at shorter or longer intervals. For example, a large bulky tumor with a partial response at first evaluation may be a reason to postpone resection, whereas bleeding tumors with evidence of progressive disease can be a reason to perform surgery within 6 weeks. Such confounding factors may have contributed to the conflicting results reported in literature, and, unfortunately, even the randomized trials to date have failed to clarify this issue [37]. The results of the Phase III multicenter randomized trial from France (GRECCAR6) demonstrated that delaying surgery for 11 weeks or more after CRT did not increase the rate of pCR after surgical resection [38]. On the contrary, the Royal Marsden trial (NCT01037049) showed that a longer (12-week) interval after CRT results in significantly higher tumor downstaging and pCR rates, and higher MRI tumor regression grade [39]. These data supported our study where patients waiting 13 weeks or more had a pCR relative risk of 2.4 compared to 6 weeks or less. Surely, a major role is played by the kinetics of tumor regression in rectal cancer. In fact, tumor regression of these tumors takes time, as reported by Dhadda and coworkers who calculated the tumor volume-halving time [27]. In their study the interval to surgery was independently associated with the percentage of tumor regression, leading to the conclusion that waiting for the highest degree of pathological response increases the R0 resection chance.

Indeed, the “interval-question” is very difficult to solve, even because the various meta-analyses did not clarified the real impact of pCR of LARC patients prognosis [6,9,10]. Furthermore, concerns about poorer TME quality in terms of fibrosis with/without more surgical technical difficulty have been raised by GRECCAR-6 and TIMING trials [31,38]. Thus, the conclusions of the paper on long term results (17-years follow-up) of the Lyon trial, considering a higher pathologic response rate as a marker but not the cause of good prognosis in rectal cancer, could be shared [40].

A further strategy to improve pCR-rate by allowing more time for tumor regression while reducing the risk of developing distant metastases is to administer systemic chemotherapy after CRT and before surgery. In this scenario, the Timing of Rectal Cancer Response to Chemoradiation Consortium (United States) published a prospective phase II trial of preoperative CRT (50.4–54 Gy with 225 mg/m<sup>2</sup>/day continuous infusion 5-FU during RT) with delayed surgery. Study group 1 underwent TME 6–8 weeks after CRT, patients in study groups 2, 3, and 4 received 2, 4, or 6 cycles of FOLFOX during the waiting period before surgery (performed 11, 15, and 19 weeks, respectively, after completion of CRT). The pCR rate of patients treated in study group 1 was 18% compared to 25%, 30%, and 38% for study groups 2–4, respectively, without increase of surgical complications [31]. The authors concluded that adding cycles of mFOLFOX6 between CRT and surgery increases the proportion of patients achieving a pCR compared to equivalent doses of systemic chemotherapy before CRT. However, they admitted that time from CRT to surgery may have had a stronger impact on pCR rate improvement compared to chemotherapy [31].

Even if the different designs of the 2 studies should be taken into account, our results in terms of pCR were comparable to the ones of Garcia Aguilar and coworkers, although no chemotherapy was prescribed in the time interval. Moreover, our result is strengthened by the unselected nature of the analyzed population. Such information, may aid the comparison with the results achieved in the selected populations recruited within randomized controlled trials. Therefore, this approach has the potential to put into a public health context the interpretation of trial findings.

Of considerable interest is the value of 1.5% improvement of pCR rate per waiting week after CRT. If confirmed by further literature data this percentage may be used in patient counseling to counteract the anxiety due to delayed surgery.

Indeed, on the basis of our analysis, the Italian radiation oncologists as well as Italian surgeons have transposed (although still with large variability) data of the international literature [23–26,31] and scientific societies guidelines [41] suggesting to delay surgery over traditional 4–6 weeks.

Several limitations of our trial deserve mentioning. The higher pCR rate observed after longer waiting periods in retrospective studies may be due to the selection of patients. In our paper, patients over a period of 20 year were included; during this long period major changes have taken place e.g. the introduction of MRI as standard imaging, the increased awareness about the importance of pCR, the trend to longer intervals, and the increased use of oxaliplatin and/or higher radiotherapy doses in CRT treatment. Therefore, the early lower pCR rate could represent a selection bias, since preoperative RT was not yet a standard of care at that time and probably mainly patients with more advanced tumors received preoperative CRT. This implies a high risk of imbalance in patient selection and type of treatment over the years.

We also reported in the results some heterogeneity among study groups in terms of clinical staging as well as pathological response evaluation (not centralized). The unexpected finding of the correlation between higher clinical stage and better response may be due to this heterogeneity. Clinical tumor stage is very error prone due to the limited accuracy of lymph node staging. The

improved imaging accuracy reached in the last ten years may have resulted in higher staging accuracy in tumor staging compared to the past. Furthermore, we should acknowledge that the definition modality of pCR is crucial for reliable data and that central review of pathological specimens is recommended in prospective trials. However, it was a retrospective observational study aimed to take a snapshot of the Italian clinical practice and to provide a background for a subsequent prospective randomized study (Bridge trial) soon being launched on a national scale. Bridge trial will be a multicenter randomized phase III trial evaluating the optimal timing between neoadjuvant CRT treatment and surgery in patients with partial/major/complete response.

Data from 21 institutes were included, resulting in an average of 100 patients per institute over 20 years. A larger sample size and/or a shorter time span would have reduced the high likelihood of considerable variety and selective inclusion (heterogeneity of the population). Moreover, the type of collected data made it impossible to provide information on surgery-related complications, treatment toxicity and survival outcomes, that were not part of the study objectives.

To date, however, this national audit allowed a multi-institutional analysis of the largest series of pathological response evaluation according to time to surgery in LARC patients ever reported in an Italian study.

In conclusion, we confirmed on a population-level that lengthening the interval (>13 weeks) from CRT to surgery improves the pathological response (pCR and pPR) in comparison to historic data. Furthermore, also radiotherapy dose >5040 cGy and two drugs chemotherapy correlated with pPR rate. These findings were probably due to technical improvement of diagnostic imaging and radiotherapy technique. Prospective randomized trials are still warranted to better define the best interval from CRT as well as the more effective radiotherapy dose and drug-schedule.

#### Authors' contributions

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#### Competing interests

The authors declare that they have no competing interests.

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#### References

- [1] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351(17):1731–40.
- [2] van de Velde CJH, Boelens PG, Borras JM, Coebergh J-W, Cervantes A, Blomqvist L, et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. *Eur J Cancer* 2014;50(1):1.e1–1.e34.
- [3] Capirci C, Valentini V, Cionini L, De Paoli A, Rodel C, Glynne-Jones R, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;72(1):99–107.
- [4] Valentini V, van Stiphout RGP, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol* 2011;29(23):3163–72.
- [5] Ortholan C, Romestaing P, Chapet O, Gerard JP. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Radiat Oncol Biol Phys* 2012;83(2):e165–71.
- [6] Zorcolo L, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A, Melis M. Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. *Ann Surg Oncol* 2012;19(9):2822–32.
- [7] Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012;99(7):918–28.
- [8] Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo L-J, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2016;11(9):835–44.
- [9] Wang XJ, Zheng ZR, Chi P, Lin HM, Lu XR, Huang Y. Effect of interval between neoadjuvant chemoradiotherapy and surgery on oncological outcome for rectal cancer: a systematic review and meta-analysis. *Gastroenterol Res Pract* 2016;2016.
- [10] Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Ann Surg* 2016;263:458–64.
- [11] Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Briffaux A, Collette L. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. *J Clin Oncol* 2005;23(24):5620–7.
- [12] Gerard J-P, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin M-T, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006;24(28):4620–5.
- [13] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;30(31):3827–33.
- [14] Rödel C, Sauer R. Integration of novel agents into combined-modality treatment for rectal cancer patients. *Strahlenther Onkol* 2007;183:227–35.
- [15] Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodigé 2. *J Clin Oncol* 2010;28:1638–44.
- [16] Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011;29(20):2773–80.
- [17] O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 2014;32:1927–34.
- [18] Schmoll HJ, Haustermans K, Rice TJ. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: disease-free survival at interim analysis. *Proc Am Soc Clin Oncol* 2014;32. abstract 3501.
- [19] Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2015;16:979–89.
- [20] Burbach JPM, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014;113(1):1–9.
- [21] Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85(1):74–80.

- [22] Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. 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* 1999;17(8):2396.
- [23] Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol* 2008;15(10):2661–7.
- [24] Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009;250(4):582–9.
- [25] Sloothaak DAM, Geijsen DE, van Leersum NJ, Punt CJA, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg* 2013;100(7):933–9.
- [26] Moore HG, Gittleman AE, Minsky BD, Wong D, Paty PB, Weiser M, et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. *Dis Colon Rectum* 2004;47(3):279–86.
- [27] Dhadda AS, Zaitoun AM, Bessell EM. Regression of rectal cancer with radiotherapy with or without concurrent capecitabine – optimising the timing of surgical resection. *Clin Oncol (R Coll Radiol)* 2009;21:23–31.
- [28] Probst CP, Becerra AZ, Aquina CT, et al. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: The key to improved tumor response and potential organ preservation. *J Am Coll Surg* 2015;221:430–40.
- [29] Kerr SF, Norton S, Glynne-Jones R. Delaying surgery after neoadjuvant chemoradiotherapy for rectal cancer may reduce postoperative morbidity without compromising prognosis. *Br J Surg* 2008;95(12):1534–40.
- [30] Tran CL, Udani S, Holt A, Arnell T, Kumar R, Stamos MJ. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. *Am J Surg* 2006;192(6):873–7.
- [31] Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. *Lancet Oncol* 2015;16(8):957–66.
- [32] Kwak Y-K, Kim K, Hoon Lee J, Hwan Kim S, Min Cho H, Yong Kim D, et al. Timely tumor response analysis after preoperative chemoradiotherapy and curative surgery in locally advanced rectal cancer: A multi-institutional study for optimal surgical timing in rectal cancer. *Radiother Oncol* 2016;119(3):512–8.
- [33] R Core Team (2016). R: a language and environment for statistical computing. R foundation for statistical computing, Vienna, Austria. URL: <https://www.R-project.org/>.
- [34] Verseveld M, de Graaf EJR, Verhoef C, van Meerten E, Punt CJA, de Hingh IHJT, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). *Br J Surg* 2015;102(7):853–60.
- [35] Habr-Gama A, Perez RO, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int J Radiat Oncol Biol Phys* 2008;71(4):1181–8.
- [36] Rödel C, Hofheinz R, Fokas E. Rectal cancer: Neoadjuvant chemoradiotherapy. *Best Pract Res Clin Gastroenterol* 2016;30(4):629–39.
- [37] Barreto SG, Sirohi B, Shrikhande SV. Timing of rectal cancer surgery following neoadjuvant chemoradiation: how close are we to striking an equipoise? *Future Oncol* 2017;13(4):303–5.
- [38] Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P, de Chaisemartin C, et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol* 2016.
- [39] Evans J, Bhoday J, Sizer B, Tekkis P, Swift R, Perez R, Tait D, Brown G. Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? *Ann Oncol* 2016;27(S6):4520.
- [40] Cotte E, Passot G, Decullier E, Maurice C, Glehen O, François Y, Lorchel F, Chapet O, Gerard JP. Pathologic response, when increased by longer interval, is a marker but not the cause of good prognosis in rectal cancer: 17-year follow-up of the Lyon R90–01 randomized trial. *Int J Radiat Oncol Biol Phys* 2016;94(3):544–53.
- [41] Friso ML, Capirci C, Turri L, Gambacorta MA, Ciabattini A, Musio D, Arcangeli G. Retto-Capitolo 5. In: Genovesi D, editor. *La Radioterapia dei Tumori Gastrointestinali - Indicazioni e Criteri Guida*. Associazione Italiana di Radioterapia; 2012, ISBN 978-88-908061-0-0. p. 119–45.