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Original Article

Timing to achieve the highest rate of pCR after preoperative radiochemotherapy in rectal cancer: a pooled analysis of 3085 patients from 7 randomized trials

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ABSTRACT

Purpose: Optimal timing of surgery after neoadjuvant chemoradiotherapy (Nad-CRT) is still controversial in locally advanced rectal cancer (LARC). The primary goal of this study was to determine the best surgical interval (SI) to achieve the highest rate of pathological complete response (pCR) and secondly to evaluate the effect on survival outcomes according to the SI.

Patients and methods: Patients data were extracted from the international randomized trials: Accord12/0405, EORTC22921, FFCD9203, CAO/ARO/AIO-94, CAO-ARO-AIO-04, INTERACT and TROG01.04. Inclusion criteria were: age≥ 18, cT3–T4 and cN0–2, no clinical evidence of distant metastasis at diagnosis, Nad-CRT followed by surgery.

Pearson's Chi-squared test with Yates' continuity correction for categorical variables, the Mann–Whitney test for continuous variables, Mann–Kendall test, Kaplan–Meier curves with log-rank test, univariate and multivariate logistic regression model was used for data analysis.

Results: 3085 patients met the inclusion criteria. Overall, the pCR rate was 14% at a median SI of 6 weeks (range 1–31). The cumulative pCR rate increased significantly when SI lengthened, with 95% of pCR events within 10 weeks from Nad-CRT.

At univariate and multivariate logistic regression analysis, lengthening of SI ($p< 0.01$), radiotherapy dose ($p< 0.01$), and the addition of oxaliplatin to Nad-CRT ($p< 0.01$) had a favorable impact on pCR. Furthermore, lengthening of SI was not impact on local recurrences, distance metastases, and overall survival.

Conclusion: This pooled analysis suggests that the best time to achieve pCR in LARC is at 10 weeks, considering that the lengthening of SI is not detrimental concerning survival outcomes.

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Preoperative radiotherapy followed by a total mesorectal excision (TME) is the standard of care for locally advanced rectal cancer (LARC) [1,2].

Long course chemoradiation and delayed surgery produces variable tumor responses, leading to a pathological complete response (pCR) between 15% and 20%. In various pooled analyses, it has been shown that tumor response has a positive correlation with multiple outcomes: local control (LC) and disease-free survival (DFS) was increased in patients with pCR [3–7]. Total mesorectal excision is still considered the standard surgical procedure in the treatment of LARC, allowing removal of both the tumor and the nodes in the perirectal fat. However, significant perioperative morbidity and, especially in the elderly, of mortality, has been associated with this surgical procedure. Also, long-term defecation and sexual dysfunctions has been more often observed with a negative impact on survivors' quality of life [8]. These observations led the radiation oncologists to investigate intensified treatment combina-

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tions, aiming to achieve an increase of CR and, consequentially, a decrease use of surgery [9,10].

Although a large number of retrospective patient series and meta-analysis showed an increased pCR rate with a longer surgical interval (SI) [11–14], while prospective trials showed controversial results [15]. Furthermore, although the quality of retrospective data is often poor, the results of single randomized trials may reflect a small population, well selected population often not representative of the whole community. To overcome these problems, in this pooled analysis of 7 randomized trials [1,16–21] LARC patients are merged in a single large database and analysed to assess any relationship between SI and pCR.

Primary objective of the present study is to detect both the optimal SI to obtain the majority of pCR and the optimal time to obtain the highest rate of pCR after neoadiuvant chemoradiation (Nad-CRT) in LARC. As second endpoint, the safety of lengthening SI regarding survival outcomes has been investigated.

Methods

Individual patient data were collected from the following international randomized trials: CAO/ARO/AIO-94 [1], EORTC22921 [16,22], FFCD9203 [17], ACCORD12/0405 [18], CAO-ARO-AIO-04 [20], TROG 01.04 [19] and INTERACT-LEADER [21].

A summary of these randomized trials included into the analysis is reported in Supplemental Material (SM).

Different treatment schedules, heterogeneous in terms of radiotherapy dose and use of preoperative and postoperative chemotherapy, were investigated. However, similar inclusion criteria were used: older than 18 years, cT3–T4 and cN0–2 stage. Patients were accrued over an extensive time period (1993–2014). From the complete set of patients treated in the different trials, patients who received preoperative radiotherapy (> 44 Gy) with concomitant chemotherapy (5-fluorouracile based regimen with or without oxaliplatin) followed by surgery were selected for the current analysis. Patients with distant metastases, short-course radiotherapy, no surgery or organ preservation approach, as well as with incomplete information about pathological specimen, surgery and radiotherapic timing, were excluded.

Tumor distance (Tdistance), defined as the distance from the ano-rectal junction to the lower edge of the tumor, was categorized as: low (less than 5 cm), medium (between 5 and 10 cm) and high (more than 10 cm). Tumor length was not included in the analyses due to the high rate of missing data (36%). The surgical procedures were categorized as low anterior resection (LAR) and abdomino-perineal resection (APR). The SI (weeks) was calculated from the end of Nad-CRT to the date of surgery. Finally, the pCR was defined as the absence of tumor cells in the surgical specimen, both at the primary tumor site and at regional lymph nodes (ypT0N0). pCR rate per week was calculated as the percentage of pCR of all the patients who received surgery each week. The cumulative pCR rate was obtained by summing the weekly pCR percentage over the SI.

Statistical analysis

Statistical analysis was performed using R version 3.3.1.

The analysis included both clinical variables as cT, cN, Tdistance and treatment variables such as radiotherapy dose, type of neoadjuvant chemotherapy, and SI. SI was considered both as a numerical and categorical variable.

Patients were stratified into two groups early surgery (eSI) and late ones (lSI), according to the median SI.

Heterogeneity between patient groups was evaluated by Pearson's χ^2 test and Mann–Whitney test for categorical and numerical variables, respectively. The trend of pCR percentage rate over the time was statistically assessed with the Mann–Kendall test, and a linear regression model with the corresponding linear coefficient was applied to quantify the correlation between the two covariates.

Univariate and multivariate logistic regression analyses were employed to identify independent predictors of pCR. Variable selection was performed using a stepwise Akaike's information criterion feature selection to determine the optimal subset of covariates. A p-value ≤ 0.05 was considered significant.

To evaluate the secondary endpoints, Kaplan–Meier curves with the log-rank test were applied to evaluate either the impact of the two groups (considering both the whole dataset and the pCR subset) on survival outcomes (LC, distant metastases (DM), DFS and overall survival (OS)) and the pCR rates of the entire dataset on survival outcomes.

Results

Data of 5247 LARC patients from 7 randomized trials treated between April 1993 and June 2014 were centrally collected. Overall, 2162 patients were excluded from the final analysis because they did not fulfill one or more inclusion criteria (SM). Therefore, data on 3085 LARC patients were considered suitable for analysis and their characteristics are shown in Table1.

The median delivered radiotherapy dose was 50.4 Gy (range 44–59.4 Gy). Considering the whole dataset, statistically significant differences were observed per trials and accrual time. In particular, 538 patients were treated from 1993 to 1998 with 46.24 Gy, 555 from 1999 to 2003 with 46.59 Gy, 1365 from 2004 to 2008 with 49.23 Gy, and 627 from 2009 to 2014 with 51.09 Gy ($p< 0.01$). Furthermore, patients underwent surgery from 1993 to 1998 at median of 5.1 weeks, from 1999 to 2003 at 5.4, from 2004 to 2008 at 6.1 weeks and from 2009 to 2014 at 6.4 weeks ($p\leq 0.01$) (Supplemental Material).

All the analyzed patients underwent surgery with a median time of 6 weeks (range, 1–31 weeks) from Nad-CRT completion. According to this, patients were divided into eSI group (1649 pts) with an interval < 6 weeks and the lSI ones with an interval $\geq$ 6 weeks (1436pts). Characteristics were homogeneous in the two groups with respect to disease stage, Tdistance, radiotherapy dose and chemotherapy type, as reported in Table1.

R0 resection was performed in 96.3% (2418 pts) of patients who had this information available. Types of surgery were APR in 839 (27.2%) patients and LAR in 2246 (72.8%) ones. No differences in sphincter-preserving surgery were found between eSI and lSI groups (74% versus 72%, $p= 0.14$), particularly in the subgroup of patients with a low rectal tumor (55% versus 55%).

Overall, pCR after Nad-CRT was achieved in 440 (14.3%) patients. The median pCR rate increased by accrual time: 10.5%, 10.2%, 14.72% and 19.9% from 1993 to 1998, 1999 to 2003, 2004 to 2008 and 2009 to 2014, respectively ($p< 0.01$).

Optimal SI to obtain the majority and the highest rate of pCR: a graphical representation of the pCR and the no pCR percentage per week are depicted in Fig. 1.

The distribution of the subset of pCR percentage over the course of the first 16 weeks is shown in Fig. 2 and a statistically significant trend was identified ($p< 0.01$) by using the Mann–Kendal test. Furthermore, a positive and a statistically significant correlation between pCR rate per week and SI is observed by applying a linear regression model (linear coefficient = 2.24 [1.53;2.95]; $p< 0.01$, $R^2 = 0.8$) (Fig. 3).

The cumulative pCR rate is shown in Fig. 4: a significant increase of cumulative pCR rate from 1% to 13% was observed between the 4th and the 11th week with the slope value of the curve of 2.13; a plateau was reached at the 16th week with a pCR rates of 14%. The 95% of all pCR events were obtained at

Table 1
Clinical-pathological characteristics.

Characteristic	All cases N° pts (%) 3085	eSI group N° pts (%) 1649 (53.5)	lSI group N° pts (%) 1436 (46.5)	*p* value
Gender				**0.022**[*]
Male	2162 (70)	1187 (54.9)	975 (45.1)	
Female	918 (29.7)	462 (50.3)	456 (49.7)	
NA	5 (0.16)	0 (0)	5 (100)	–
Median age years (range)	62 (22–83)	62 (24–82)	62 (22–83)	**0.033**[a]
NA	19 (0.006)	0 (0)	19 (0.006)	
cT stage				0.99[*]
cT3	2880 (93)	1540 (53.5)	1340 (46.5)	
cT4	205 (7)	109 (53.1)	96 (46.9)	
NA	0 (0)	0 (0)	0 (0)	–
cN stage				**<0.01**[*]
cN0	839 (27)	500 (59.6)	339 (40.4)	
cN+	1621 (52.5)	737 (45.5)	884 (54.5)	
NA	625 (20)	412 (65.9)	213 (34.1)	–
Stage disease				**<0.01**[*]
II	839 (27)	500 (59.6)	339 (40.4)	
III	1621 (52.5)	737 (45.5)	884 (54.5)	
NA	625 (20)	412 (65.9)	213 (34.1)	
Tumor location				**<0.01**[*]
Low	1188 (38.5)	686 (57.7)	502 (42.3)	
Medium	1339 (43.4)	791 (59.1)	548 (40.9)	
High	433 (14)	121 (27.9)	312 (72.1)	
NA	125 (4)	51 (40.8)	74 (59.2)	–
Median RT dose (Gy) (range)	50.4 (44–59.4)	50.4 (44–59.4)	50.4 (44–58)	**<0.01**[*]
CT schedule				**<0.01**[*]
5-Fu/ Cap	2127 (70)	1209 (56.8)	918 (43.2)	
Oxa based	958 (31)	440 (45.9)	518 (54.1)	
NA	0 (0)	0 (0)	0 (0)	–
Surgery				0.41[*]
APR	839 (27.2)	459 (54.7)	380 (45.3)	
LAR based	2246 (72.8)	1190 (53)	1056 (47)	
NA	0 (0)	0 (0)	0 (0)	–

eSI: early surgical interval; lSI: late surgical interval; NA: not available; RT: radiotherapy; CT: chemotherapy; 5Fu: 5-fluorouracil; Cap: capecitabine; Oxa: oxaliplatin; APR: abdominal-perineal resection; LAR: low anterior resection.
[*] Pearson's χ^2 test.
[a] Mann–Whitney test.

10th week. Analyzing the curve from the 11th week, a multiplication factor of 0.035 was obtained. Considering the two groups, the cumulative pCR rates were 11.6% and 18.8% in the eSI and lSI group, respectively ($p< 0.01$). lSI patients had a 1.58 (95% C.I. 1.33–1.88) relative incidence of pCR compared to eSI group. After the first sixteen weeks no significant amount of pCR events is detected.

At univariate analyses, cT ($p= 0.03$) and Tdistance ($p< 0.01$) significantly correlated with pCR rate, while no correlation was found with cN ($p= 0.67$). cT3 and the medium–high tumor had a higher probability to achieve pCR. Furthermore, considering the SI as a continuous variable, there was a significant association between longer SI and pCR rate ($p< 0.01$). Moreover, the intensification of treatment in terms of radiotherapy dose ($p< 0.01$) and chemotherapy with oxaliplatin ($p< 0.01$) was associated with a higher pCR rate. At multivariate analysis cT, SI and oxaliplatin continued to be correlated with pCR (Table 2).

The median follow-up was 54.8 months (range 0–212). Overall, 322 (10.4%) patients developed local recurrence (LR). The 5-year LC rate was 87%. No significant difference in terms of LR was recorded between the eSI and lSI group (86% versus 87%, $p= 0.53$) (Supplemental Material).

A total of 828 (26.8%) patients developed DM. The 5-years metastases-free survival rate was 70%, without significant differences between the two groups (70% versus 69%, $p= 0.83$).

The 5-years DFS rate was 66% and no significant differences were observed between the two groups (65% versus 66%, $p= 0.65$).

Finally, at the time of this analysis, 670 (22%) patients died. The 5-years OS was 78%; no statistical difference was recorded between the groups (78% versus 78%, $p= 0.64$).

Patients with pCR had significant better 5-years LC (96% vs 85%, $p< 0.01$), DM (89% vs 67%, $p< 0.01$), DFS (85% vs 63%, $p< 0.01$) and OS (91% vs 76%, $p< 0.01$) compared to not complete responders (Supplemental Material). Analyzing the subset of patients who achieved a pCR, no differences in terms of LR, DM, DFS and OS between the eSI and the lSI groups were found ($p= 0.7$) (Supplemental Material).

Discussion

During the last decades, the role of pCR as a prognostic marker has been extensively investigated [3–7,22]. It is nowadays evident that complete responder patients after neoadjuvant treatment have a better prognosis, compared to non-responders.

Although it can be debated whether achievement of pCR is the expression of a favorable tumor biology, regardless of treatment, or rather it is the pCR result the responsible for better oncological outcomes. However, one of the major goals in the treatment of LARC patients is to achieve the highest possible number of com-

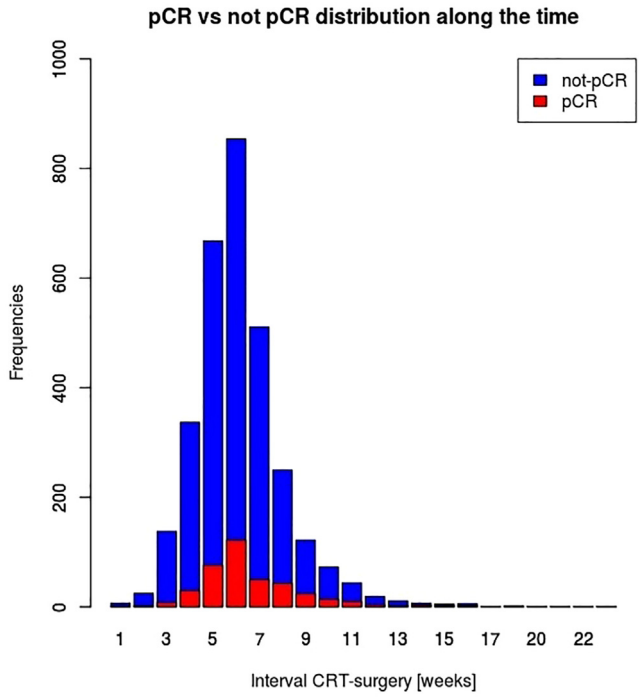

Fig. 1. Representation of the pCR and the no pCR percentage per week. pCR: pathological complete response.

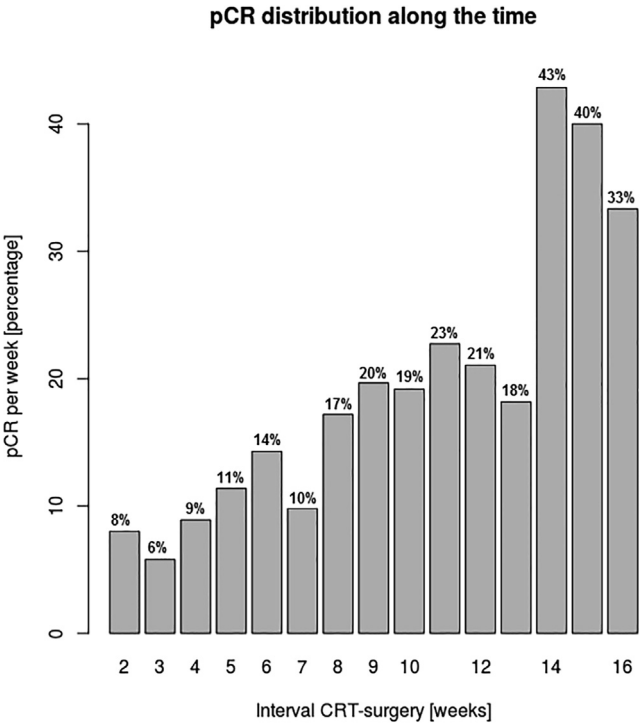

Fig. 2. pCR percentage per week. pCR: pathological complete response; CRT: chemoradiotherapy.

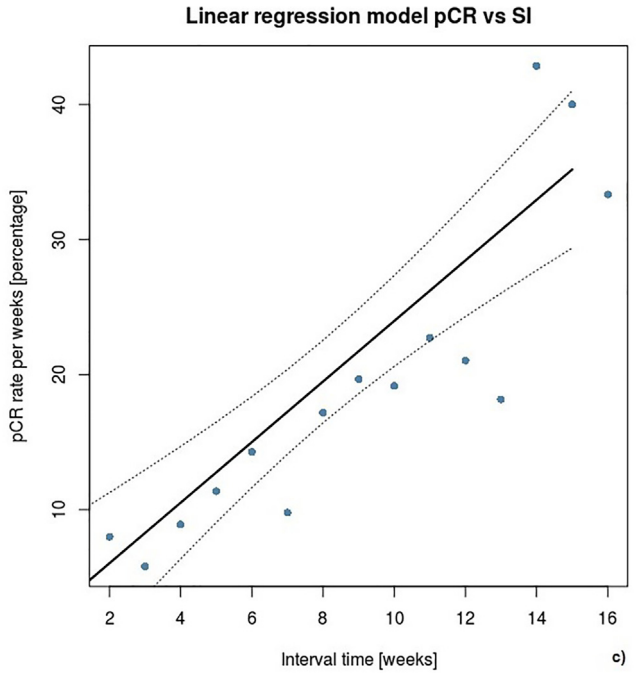

Fig. 3. Linear regression model correlation between pCR rate per week and SI. pCR: pathological complete response; SI: surgical interval.

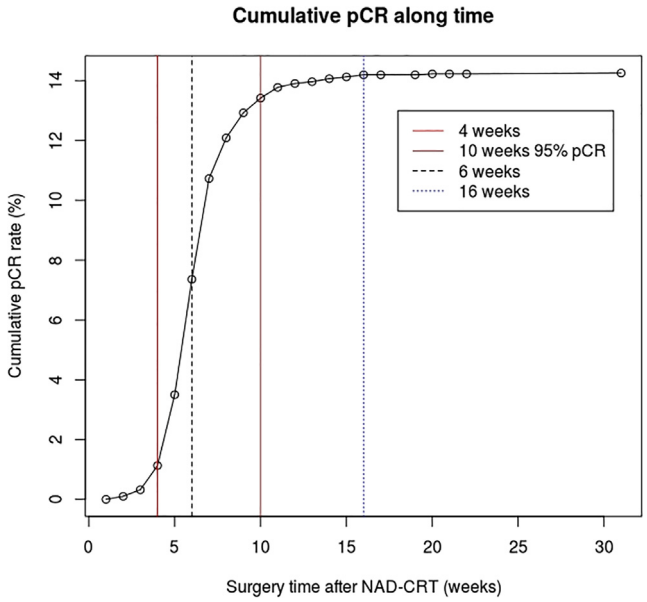

Fig. 4. Cumulative pCR rate. pCR: pathological complete response; NAD-CRT: neoadjuvant chemo-radiotherapy.

plete response (CR), by modulating preoperative treatment procedures, particularly in organ preservation strategies. Different strategies have been investigated over the last 15 years by both increasing the radiotherapy dose and/or intensifying preoperative chemotherapy [20,23,24]. Lengthening of the time interval before surgery has recently been shown to be a third cornerstone for achieving higher numbers of downstaging and pCR [13,14,25]. Despite that some studies show a controversial results of lengthening the time interval before surgery, either in terms of increasing the pCR rate or controlling surgical morbidity and perioperative complications [15,26,27], there is sufficient published evidence to suggest that a greater delay to surgery following completion of preoperative therapy is associated with an increased likelihood of achieving a pCR [25,28–30]. The Lyon trial was the first randomized trial to show that a longer interval (2-week versus 6-week delay), between Nad-CRT and surgery, provides increased tumor downstaging. The results of this study reinforced the recommendation of a 6–8 week-long delay. A SI of 10–11 weeks was

Table 2
Univariate and multivariate analyses for pathologic complete response (pCR) according to treatment variables.

Variable Name	pCR			
	Univariate		Multivariate	
	Coefficient	*p* Value	Coefficient	*p* Value
SI (as continuous variable)	0.1336	*p* < **0.01**	0.131	*p* < **0.01**
RT Dose	0.0615	*p* < **0.01**	–	–
OXI based-CT	0.4400	*p* < **0.01**	0.366	*p* < **0.01**
Tumor Distance	0.010	*p* < **0.01**	–	–
cT	-0.5	p= **0.03**	-0.49	p=**0.04**
cN	0.05	p= 0.7	–	–

SI: surgical interval; RT: radiotherapy; CT: chemotherapy; OXI: oxaliplatin; pCR: pathological complete response.
[a]Significant *p* values (*p* value <= 0.05) are in bold.
[b]Only variables with a *p* value <0.05 in the univariate logistic regression analysis were included in the multivariate model.

investigated when a higher number of pCR is aimed for [11,30]. Recent studies reported that a waiting time of 13 weeks or more correlates with a higher rate of pCR in LARC patients with [31] or without [12] a chemotherapy intensification. Despite this evidence, the heterogeneity of the waiting time cutoff, used in the different studies, does not allow to identify the better time for restaging and surgery.

Furthermore, one of the major concerns of lengthening the SI is a potential detrimental effect in terms of survival outcomes.

In this setting, a pooled analysis on 3085 patients from 7 clinical randomized trials related to rectal cancer [1,17,19–22,32] has been performed with the primary aim to detect both the optimal SI to obtain the majority of pCR, and the optimal time to obtain the highest rate of pCR. As second endpoint the safety of a lengthening of the interval on survival outcomes has been investigated. A statistically significant positive trend of pCR percentage over the weeks was established until sixteen weeks. Furthermore, the longer SI increased the cumulative rate of pCR from 4 to 10 weeks when the 95% of pCR events were detected. Using the median SI of 6 weeks as cut-off to divide patients in eSI and lSI group, a significant advantage in terms of pCR for patients undergone delayed surgery (11.6% versus 18.8%) was observed, with a relative risk of achieving a pCR of 1.62 for the lSI compared to the eSI. If these results are in line with the literature stating, it is interesting to know that the response of the tumor to the Nad-CRT is continuing over the time with the highest rate of pCR after 10 weeks. Undoubtedly, a significant role is played by the kinetics of tumor regression in rectal cancer. Dhadda et al. calculated the median-volume halving time for rectal cancer of 14 days, concluding that for an average sized tumour (54 cm^3) a 20 weeks SI is needed to achieve a complete tumor regression [33]. The same topic was previously investigated in large data analyses, obtaining overlapping results [13,14]. In particular, Sloothaak and coworkers reported a correlation between the CRT-surgery interval and pCR, in more than 1500 patients [13]. Although our results follow those published by these Authors, some differences between the two analyses exist and may be useful to better understand the role of the interval as influencer of tumor response in rectal cancer. The nature of the data is the first aspect to be considered. The Sloothaak series consider data coming from Holland and all-around Europe, being a registry analysis, while in our series, data are prospectively collected in randomized clinical trials [13]. Furthermore, the Dutch trial's selection criteria included a more advanced stage; and finally, the interval measurement's time point was set at the radiotherapy start and at the radiotherapy end in the Dutch experience and in ours, respectively.

Considering survival outcomes, the lengthening of SI did not appear detrimental in terms of LR, DM, DFS and OS, being in line with the existing literature. However, prolongation of SI had no a statistical impact on survival outcomes. Within the subgroup of pCR patients no differences were observed, suggesting a similar intrinsic characteristic of the tumor response, regardless of the SI. Interestingly, 10% in LR rate is a bit higher than expected. This result might be derived from the not routine use of either TME in some of the trial and/or of magnetic resonance imaging (MRI): both, with different mechanisms, could have contributed to leave behind some microscopic cancer cells in the tumor bed.

This analysis can be even more interesting if we consider the possibility to identify patients with a good prognosis to better personalize the treatment. Over the past decade, the oncological treatment has gradually shifted towards a more individualized strategy, with the aim of improving long-term quality of life and functional outcomes. This approach has led to a growing interest also in organ-preserving strategies especially in a strictly selected population where surgery could lead to temporary or permanent colostomy and serious long-term morbidity, such as urinary and sexual dysfunction. An International Watch & Wait Database has been established in February 2014 with the aim to gain more evidence supporting organ preserving strategies considering that randomized controlled trials for this indication are lacking and challenging for both ethical and practical reasons [34]. The possibility to have both a better idea of the optimal time to obtain the highest rate of CR and a safer evidence that a longer SI is not detrimental in terms of survival outcomes, can be an important evidence supporting the safety and feasibility of an organ preservation strategy.

Finally, even considering the importance of this analysis, its limits needs to be mentioned. The pooled analysis does not include all randomized trial published in the field of rectal cancer, hence some information could have been missed, even though the number of pooled patients might be considered sufficient for the present analysis. The analyzed studies cover an inclusion period of about 20 years. The improvement of techniques and surgical procedures with the introduction of TME, the standard use of MRI as diagnostic imaging modality, the improvement of radiotherapic technique permitting dose escalation programs, the increased combination of chemotherapy with CRT treatment, the growing awareness about the importance of pCR and the trend to longer intervals, are only some of the numerous significant changes that have been taken place over the years. As a demonstration, our pooled analysis makes the time effect on pCR evident, which significantly increased from 10.5% to 19% from 1993 to 2014.

These differences, due to time-effect, are also reflected by the imbalance in patient selection and type segregated in the two groups. In fact, the two groups were not homogeneous respecting to radiotherapy dose ($p< 0.01$) and kind of chemotherapy ($p< 0.01$). Although the role of radiotherapy dose and chemotherapy intensification seems to be confirmed in the univariate analysis as a cause of higher pCR, at the multivariate analyses the only significant variables are chemotherapy with oxaliplatin, and SI.

In conclusion, our results show that prolonging the interval between Nad-CRT and surgery increases the pCR rate, while it is not detrimental to long-term outcomes. The data suggest that at least 10 weeks should be considered to achieve 95% of all pCR events. Although to date many patients can be offered 'watch and wait' or other organ sparing-strategies, the prolongation of SI, by improving quality of life and maintaining excellent long-term outcomes, has to be mandatory considered in LARC treatment.

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Provision of study materials or patients: van Soest J., Collette L., Gérard JP., Ngan S.Y., Rödel C., Dekker A. and Vincenzo Valentini.

Collection and assembly of data: Masciocchi C, Chiloiro G, van Soest J., Collette L., Gérard JP., Ngan S.Y., Rödel C., Damiani A. and Vincenzo Valentini.

Data analysis and interpretation: Gambacorta MA, Masciocchi C, Chiloiro G, van Soest J., Damiani A., Dekker A. and Vincenzo Valentini.

Not Disclaimers.

Conflict of Interest Statement/Declaration of Interest

The work has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.09.026.

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