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# Long-term outcomes in ypT0 rectal cancers: An international multi-centric investigation on behalf of Italian Society of Surgical Oncology Young Board (YSICO)

L. Lorenzon [a,*], D. Parini [b], D. Rega [c], A. Mellano [d], V. Vigorita [e], A. Biondi [f], R. Jaminez-Rosellon [g], M. Scheiterle [h], I. Giannini [i], G. Gallo [j,k], G. Marino [l], L. Turati [m], P. Marsanic [d], L. De Franco [h], L. Marano [n], Senior SICO Supervising Members, R. De Luca [o]

[a] *Surgical and Medical Department of Translational Medicine, Sant'Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy*

[b] *General Surgery Unit, Santa Maria della Misericordia Hospital, Rovigo, Italy*

[c] *Colorectal Surgical Oncology, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione Giovanni Pascale IRCCS, Naples, Italy*

[d] *Surgical Oncology Unit, Candiolo Cancer Institute – IRCCS – Candiolo Cancer Institute – IRCCS, Turin, Italy*

[e] *Unit of Coloproctology, Department of General and Digestive Surgery, University Hospital Complex of Vigo Alvaro Conquieiro Hospital, Vigo, Spain*

[f] *General Surgery Unit, Fondazione Policlinico Universitario Agostino Gemelli, Catholic University, Rome, Italy*

[g] *Digestive Surgery Unit, University Hospital La Fe, Valencia, Spain*

[h] *Department of Medicine, Surgery and Neurosciences – Unit of General Surgery and Surgical Oncology, University of Siena, Italy*

[i] *General Surgery Unit, Policlinico Bari, Italy*

[j] *Coloproctology Unit, Santa Rita Clinic, Vercelli, Italy*

[k] *Department of Medical and Surgical Sciences, University of Catanzaro, Italy*

[l] *Surgery Unit, IRCCS CROB Regional Oncologic Center, Rionero in Vulture, Potenza, Italy*

[m] *Surgical Oncology Unit, Treviglio Hospital, ASST Bergamo Ovest, Italy*

[n] *Multidisciplinary Robotic Surgery Unit, "San Matteo degli Infermi Hospital" – ASL Umbria 2, Spoleto, Perugia, Italy*

[o] *Department of Surgical Oncology, National Cancer Research Centre, Istituto Tumori Giovanni Paolo II, Bari, Italy*

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## Abstract

*Aim*: To investigate the outcome and pattern of survivals of rectal cancer patients presenting a complete or nearly complete tumor response after neo-adjuvant treatment.

*Methods*: Young surgeons <40 years old affiliated to the Italian Society of Surgical Oncology (YSICO) from 13 referral centers for colorectal cancer treatment, were invited to participate a retrospective study. Records from patients treated from 2005 to 2015 with a pathological diagnosis of ypT0/ypTis were retrieved and pooled in a common data-base for statistical purposes. All clinical and pathological variables were reviewed. Univariate and multivariate analyses were conducted with the end-point of survivals.

*Results*: Two hundreds and sixty-one patients were analyzed including 237 ypT0 and 24 ypTis. Nodal positive patients were 8.7%. More than sixty-six percent of the patients did not perform adjuvant chemotherapy, with a statistical difference comparing N0 versus N+ patients (66.8% *vs* 40.9%, p 0.02). Mean follow-up was of 47.6 months. Twenty-two relapses were observed, 91.6% at a distant site. The mean time to recurrence was of 35.3 months. On univariate analysis, the use of adjuvant chemotherapy correlated with better OS exclusively in

* Corresponding author. Surgical and Medical Department of Traslational Medicine, Faculty of Medicine and Psychology, "Sapienza" University of Rome, St. Andrea Hospital, Via di Grottarossa 1035-39, 00189 Rome, Italy. Fax: +39 0633775322.
*E-mail address:* laura.lorenzon@uniroma1.it (L. Lorenzon).

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ypT0N + patients and not in ypT0N0. Univariate and multivariate analyses documented nodal positivity as the only prognostic factor correlated with a worse OS.

*Conclusion*: Recurrences were mostly diagnosed at a distant site and within the third year of follow-up. Nodal positivity was the only variable independently correlated with a worse OS. Univariate analysis documented a benefit for the use of adjuvant chemotherapy treatment exclusively in ypT0N + rectal cancers.



*Keywords:* Rectal cancer; Neo-adjuvant treatment; Pathologic complete response; ypT0

## Introduction

Colorectal cancer (CRC) is the second most frequent diagnosed cancer and the second cause of cancer-related death in European countries with an incidence of about 450.000 new cases each year[1]: rectal cancer accounts for about 30% of CRCs.[2] Over the last 30 years the approach to rectal cancer changed and become multimodal as a result of the researches focused on its biological and clinical behavior. The improvements lead to the introduction of neo-adjuvant (chemo)radiation treatments (NAT)[3–7] and the standardization of the total mesorectal excision (TME) surgical technique.[8,9]

Currently, the latest guidelines from the European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) recommend to perform NAT in mid-low locally advanced, non-metastatic rectal cancers, clinically staged as $\geq$ T3 any N, anyT N+ or if the circumferential resection margin (CRM) is assessed less than 1 mm. This approach resulted in higher chances of tumor down-sizing and down-staging and in the reduction of local recurrences.[10] The ultimate effect of NAT by tumor down-staging is the achievement of a complete response, which may be defined as clinical (absence of residual primary tumor clinically detectable, cCR − cT0) or pathological (absence of viable tumor cell within the rectal wall, after full pathologic examination of the surgical specimen, pCR − ypT0).[11] Interestingly, pCR occurs in approximately 20% of patients who underwent NAT.[12]

It should be emphasized that, in European countries, the change of practice in the use of NAT can be ascribed around the 1990s[13] and became widespread afterwards. Therefore, literature about complete responders started to emerge over the last 15 years and is mostly based on scant observational case series.

Although recently few retrospective pooled data analyses[12,14–17] and systematic reviews-meta-analyses[18–20] were published, definitive results in this field are still lacking. Indeed, there are no robust markers predictive of pCR (molecular, clinical or radiological),[19] a number of surgical approaches have been considered (from local excisions to formal rectal resection)[14] and there is no consensus regarding the appropriateness of adjuvant treatment following surgical resection.[16]

Another main issue is the presence of residual cancerous cells within lymph-nodes harvested in the specimen of a rectal resection, even when a complete regression of the primary tumor has been achieved (ypT0N+). These patients account for the 6.7–17.4%[12,21] of ypT0 and are seldom analyzed. However, their identification is crucial to optimize surgical strategy in order to avoid over or under treatments.

Despite ypT0 patients have been reported with favorable outcomes[22] additional issues still need to be defined such as timing and pattern of recurrence and follow up strategies. On these bases, a multi-centric retrospective study has been designed to analyze a large sample of ypT0. The primary aims of this research were to investigate the clinical and pathologic data, treatment modalities and long term outcomes of rectal cancer patients presenting with complete pathologic response following surgical resection.

## Patients and methods

### *Study design*

The study protocol was conceived to involve young surgeons ($\leq$40 years old) from colorectal cancer referral centers affiliated to the Italian Society of Surgical Oncology (YSICO) in a network of research and partnership. Thirteen centers agreed to participate with a YSICO investigator for data collection and a senior SICO member for mentorship and quality data validation (Senior SICO Supervising Members).

This study received the approval by the SICO colorectal scientific board and by the ethical committee (IRB protocol 4051_2016). Inclusion criteria was a pathologic diagnosis of primary rectal cancer with complete (ypT0) or nearly complete (ypTis) tumor response after NAT, treated over the last 10 years (2005–2015) independently from NAT protocol, type of surgical treatment performed or nodal *status.* All the clinical and pathological records were pooled anonymously in a common database for statistical purposes.

### *Data collection*

Demographic data, tumor location and diameter, presence or not of large bowel obstruction, type of radiological work-up based on Computer Tomography scan, Magnetic Resonance Imaging (MRI) or Endoscopic Ultrasound (Endo-

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US), clinical staging (cTNM) and NAT protocols were retrieved and extensively analyzed. Patients were categorized for NAT if treated with a short-course radiotherapy (Short RT) or a long-course chemo-radiotherapy (CHT-RT) protocol. The total dose of radiation was recorded (Gy), along with possible dose reductions or treatment interruptions. Radiological assessments following NAT (complete response – CR, major response – MR, partial response – PR and non-response – NR) were also recorded together with the interval time to surgery. With respect to the surgical strategies, low-anterior resection, abdomino-perineal resection and trans-anal TME (TA-TME) were categorized as TME procedures. On the same extent, those patients who underwent a trans-anal endoscopic microsurgery (TEM) resection, a trans-anal minimal invasive (TAMIS) resection or traditional transanal excision (TAE), were all grouped in the local excision (LE) category. Endoscopic biopsies before neo-adjuvant treatment were not collected, thus molecular analyses were not performed, nor were available. Records included also pathologic data (N stage, number of positive nodes, lymph-nodes harvested in the surgical specimen – LNH, mesorectal quality), rate of adjuvant chemotherapy treatment (CT) and long term oncological outcomes.

### *Follow-up*

Follow-up of the patients was conducted with the end-points of overall survival (OS, any cause of death), disease free survival (DFS, first recurrence after surgical resection) and disease specific survival (DSS, death related to rectal cancer).

### *Statistical analysis*

Continuous variables were analyzed using means and standard deviations (SD), whereas categorical variables were analyzed using frequencies and percents and compared using Chi-square test. Survival analyses were conducted using the Kaplan–Meier method with log-rank test and Cox regression analysis (stepwise method). Univariate survival analyses were aimed to evaluate the following co-variates: nodal *status* (N+ *vs* N0), tumor location (>5 cm *vs* < 5 cm), clinical/endoscopic stenosis (presence *vs* absence), surgical approach (TME *vs* LE), neo-adjuvant treatment (CHT-RT *vs* Short RT). All statistical analyses were obtained using MedCalc (MariaKerke, Belgium) and SPSS (IBM, Armonk USA) software. All tests were performed two-tailed and a p value $< 0.05$ was considered as statistically significant.

## Results

### *Patients*

Two-hundred and eighty-five patients from 13 Institutions (11 Italians and 2 Spanish) were reviewed. Interestingly, 12 out of the 13 centers participating in the study could be defined as high volume centers for colorectal cancer treatment.[23]

Upon review of the clinical records, 24 patients were excluded because of: evident systemic metastases (9 patients), uncertain systemic metastases (2 patients), chemotherapy-only NAT treatment (6 patients), refusal of surgical procedures after a macro-biopsy consistent with complete tumor regression (2 patients), peri-operative death (2 patients) and lost at follow-up (3 patients). Eventually 261 patients (237 ypT0 and 24 ypTis) were included and analyzed, Fig. 1.

The vast majority of the patients enrolled were males (M/F 1.8); mean age was of 63.7 years and tumors were located mainly in the low-rectum (mean distance from the anal verge 5.7 cm; SD 2.9), Table 1.

Ninety percent of the patients were locally staged using MRI, which was the procedure of choice also for re-staging assessment. The majority of the tumors were clinically assessed as cT3 (77.6%), cN+ (84.4%), CRM negative (80.3%).

Two hundred thirty-seven patients (90.8%) were treated using CHT-RT while 24 patients (9.2%) received Short RT. Those patients treated with CHT-RT received radiation and concomitant oral/i.v. fluoropirimidine according to international recommendations.[24] Dose reductions were reported just in 19 patients and the median radiation dose in the CHT-RT group was of 50.4 Gy. Indeed, 95.0% of the CHT-RT treatments were based on a dose ranging from 50.4 to 56.0 Gy; about 2.2% of the patients received less than 50.0 Gy and 2.7% more than 56.0 Gy. Furthermore, in the CHT-RT group, the mean interval to surgery was of 9.5 weeks (Table 1), as 71.6% of these patients were treated ranging from 6 to 12 weeks following NAT. The 11.0% of this series was treated within the 6th weeks and about 16.0% after the 12th weeks. Longer intervals were related to patient hesitations or a management issue in scheduling surgery. Short course RT was followed by immediate surgery in 5 cases, whereas 19 patients (79.1% of this group) were treated according to a protocol for Short RT followed by delayed surgical resection at a single Institution.[25]

TME operations accounted for the 96.2% of the procedures and 99.0% of the specimens reported a mesorectal integrity. In TME resections the mean lymph node harvest (LNH) was 11.2 and 8.7% were reported as ypT0N + patients (Table 2).

### *Outcomes*

Adjuvant CT was not administered in 66.5% of the patients (Table 2). However, the rate of N0 patients who did not complete adjuvant treatment was significantly higher compared with that of N1 patients (respectively 66.8% *vs* 40.9%, Chi-square p 0.02). Mean follow-up was 47.6 months, median 45.0 months. Overall, 22 relapses have

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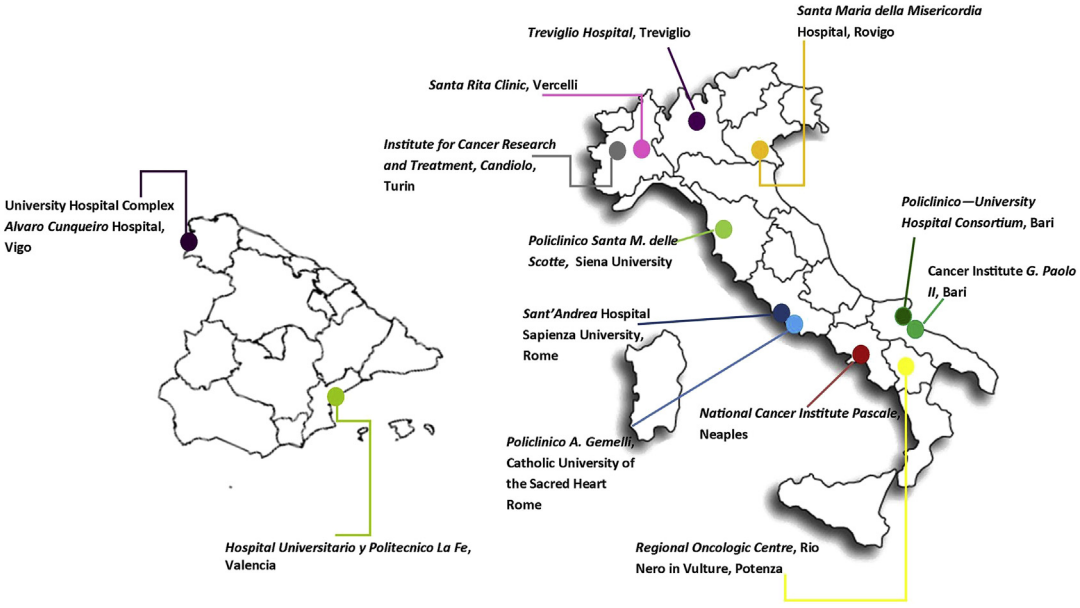


| n | Center | n of patients | Short Course RT | Long Course CHT-RT |
|---|---|---|---|---|
| 1 | CROB Regional Oncologic Center, Rionero in Vulture - Italy | 4.0 | 1.0 | 3.0 |
| 2 | Treviglio Hospital - Italy | 4.0 | 0.0 | 4.0 |
| 3 | Santa Rita Clinic, Vercelli - Italy | 5.0 | 0.0 | 5.0 |
| 4 | Policlinico Bari - Italy | 8.0 | 0.0 | 8.0 |
| 5 | University of Siena - Italy | 9.0 | 0.0 | 9.0 |
| 6 | Sant'Andrea Hospital, Rome - Italy | 15.0 | 1.0 | 14.0 |
| 7 | National Cancer Research Centre Istituto Tumori Giovanni Paolo II, Bari - Italy | 20.0 | 0.0 | 20.0 |
| 8 | University Hospital La Fe, Valencia - Spain | 23.0 | 0.0 | 23.0 |
| 9 | Fondazione Policlinico Universitario Agostino Gemelli, Rome - Italy | 26.0 | 1.0 | 25.0 |
| 10 | University Hospital Complex of Vigo Alvaro Conquieiro Hospital, Vigo - Spain | 27.0 | 0.0 | 27.0 |
| 11 | Candiolo Cancer Institute- IRCCS, Turin - Italy | 35.0 | 2.0 | 33.0 |
| 12 | Fondazione Giovanni Pascale IRCCS, Naples - Italy | 42.0 | 19.0 | 23.0 |
| 13 | Santa Maria della Misericordia Hospital, Rovigo - Italy | 43.0 | 0.0 | 43.0 |
| **Total** | | **261.0** | **24.0** | **237.0** |

Figure 1. Italian and Spanish YSICO affiliated Institutions participating in the study and related ypT0 volumes.

been observed, 91.6% localized at a distant site, mostly in lung (45.4%) and liver (36.4%). Notably, all pulmonary metastases occurred in low ypT0N0 rectal cancers (≤4 cm from the anal verge). The mean time to recurrence was 35.3 months (Table 2). Twelve out of 22 patients who relapsed underwent adjuvant CT. Of note, all patients who recurred locally had a pathological specimen consistent with ypT0N0.

Fig. 2 reports Kaplan–Meier survival curves of TME patients, showing results in relation to the nodal *status* (N0 *vs* N+ patients log rank test OS p 0.035). Furthermore, the use of adjuvant CT in relation to patient OS was investigated in nodal ypT0N + *vs* ypT0N0 patients. This latter analysis documented that ypT0N + patients undergone adjuvant CT had more favorable OS outcomes comparing ypT0N + who did not performed any chemotherapy following surgery (log rank test p 0.03). Opposite, ypT0N0 OS seemed not to be affected by the use of adjuvant CT.

Both on univariate and multivariate analyses, a nodal positivity was the only prognostic factor statistically correlated with a worse OS: in particular ypT0N + patients were 4.48 more likely to have OS event than ypT0N0 patients, Fig. 3.

## Discussion

Complete tumor regression is a milestone achievement in the field of rectal cancer therapy and is the results of three decades of clinical studies. It has been described in

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Table 1
Clinical features and treatment modalities of ypT0 patients.

| | |
|---|---|
| **Age (years)** | |
| Mean; SD | 63.7; 10.9 |
| Median | 66.0 |
| Range | 24.0–86.0 |
| **Sex – n (%)** | |
| M | 169.0 (64.8) |
| F | 92.0 (35.2) |
| M/F | 1.8 |
| Tot | 261.0 (100.0) |
| **Location (cm from the anal verge)** | |
| Mean; SD | 5.7; 2.9 |
| Median | 5.0 |
| Range | 0.1–15.0 |
| **Tumor Diameter (cm)** | |
| Mean; SD | 4.9; 2.5 |
| Median | 4.5 |
| Range | 0.8–22.0 |
| **Stenosis – n (%)** | |
| Yes | 36.0 (15.2) |
| No | 201.0 (84.8) |
| Tot | 237.0 (100.0) |
| **cT – n (%)** | |
| cT1-cT2 | 39.0 (15.1) |
| cT3 | 201.0 (77.6) |
| cT4 | 19.0 (7.3) |
| Tot | 259.0 (100.0) |
| **cN – n (%)** | |
| cN0 | 85.0 (32.9) |
| cN+ | 173.0 (67.1) |
| Tot | 258.0 (100.0) |
| **NAT – n (%)** | |
| CHT-RT | 237.0 (90.8) |
| Short Term RT | 24.0 (9.2) |
| Tot | 261.0 (100.0) |
| **Dose Reduction CHT-RT – n (%)** | |
| Yes | 19.0 (8.1) |
| No | 217.0 (91.9) |
| Tot | 246.0 (100.0) |
| **Dose Reduction Short Term RT – n (%)** | |
| Yes | 1.0 (4.2) |
| No | 23.0 (95.8) |
| Tot | 24.0 (100.0) |
| **Mean RT CHT-RT (Gy)** | |
| Mean; SD | 52.1; 2.8 |
| Median | 50.4 |
| Range | 38.6–58.0 |
| **Interval to surgery CHT-RT (weeks)** | |
| Mean; SD | 9.5; 3.6 |
| Median | 9.0 |
| Range | 3.0–25.0 |
| **Re-Staging Assessment – n (%)** | |
| Complete Response | 42.0 (17.8) |
| Major Response | 96.0 (40.7) |
| Partial Response | 93.0 (39.4) |
| Non Responders | 5.0 (2.1) |
| Tot | 236.0 (100.0) |
| **Surgical Approach – n (%)** | |
| Low Anterior Resection | 195.0 (74.7) |
| Abdomino-Perineal Resection | 42.0 (16.1) |
| TA-TME | 14.0 (5.4) |
| TEM-TAMIS-OTHER LE | 10.0 (3.8) |
| Tot | 261.0 (100.0) |

Table 2
Pathologic data and outcome of ypT0 patients.

| | |
|---|---|
| **Mesorectal Quality – n (%)** | |
| Intact Mesorectal Fascia | 199.0 (99.0) |
| Interrupted Fascia | 2.0 (1.0) |
| Tot | 201.0 (100.0) |
| **ypT – n (%)** | |
| ypT0 | 237.0 (90.8) |
| ypTis | 24.0 (9.2) |
| Tot | 261.0 (100.0) |
| **ypN – n (%)** | |
| ypN0 | 232.0 (91.3) |
| ypN+ | 22.0 (8.7) |
| Tot | 254.0 (100.0) |
| **LNH** | |
| Mean; SD | 11.2; 6.9 |
| Median | 10.0 |
| Range | 1.0–37.0 |
| **Adjuvant CT –n (%)** | |
| Yes | 86.0 (33.5) |
| No | 171.0 (66.5) |
| Tot | 257.0 (100.0) |
| **Follow-up – DSS (months)** | |
| Mean; SD | 47.6; 33.7 |
| Median | 45.0 |
| Range | 2.0–129.0 |
| **Relapse –n (%)** | |
| Yes | 22.0 (8.4) |
| No | 239.0 (91.6) |
| Tot | 261.0 (100.0) |
| **Relapse Pattern** | |
| Distant | 17.0 (81.0) |
| Local | 4.0 (19.0) |
| Tot | 21.0 (100.0) |
| **Time to recurrence (months)** | |
| Mean; SD | 35.3; 34.2 |
| Median | 23.5 |
| Range | 2.6–129.0 |

about 20% of patients treated with a NAT.[12] Indeed, the objective of neo-adjuvant treatments could be summarized in: a) reducing the risk of local relapses (down-staging) and b) improving resectability, R0-resections and sphincter-saving procedures (down-sizing). Treatment modalities usually include Short RT (5 × 5 Gy scheme) followed by immediate surgery or a CHT-RT protocol of 50.4 Gy administered in 25–28 fractions combined with fluoropyrimidine chemotherapy, with surgery performed after an interval of at least 4 weeks.[10] Short RT approach has clear advantages such as simpler management and reduced costs. However downsizing and downstaging are not usually considered after Short RT because of the short interval to surgery. Several investigations are now ongoing to explore the potential down-staging effect of Short RT followed by delayed surgery.[10,25,26] On the other hand, CHT-RT offers higher chances of down-sizing including more pCRs, improved resectability, higher rate of sphincter-saving procedures, low rates of local relapse and improved long-term survivals (comparing with preoperative radiotherapy

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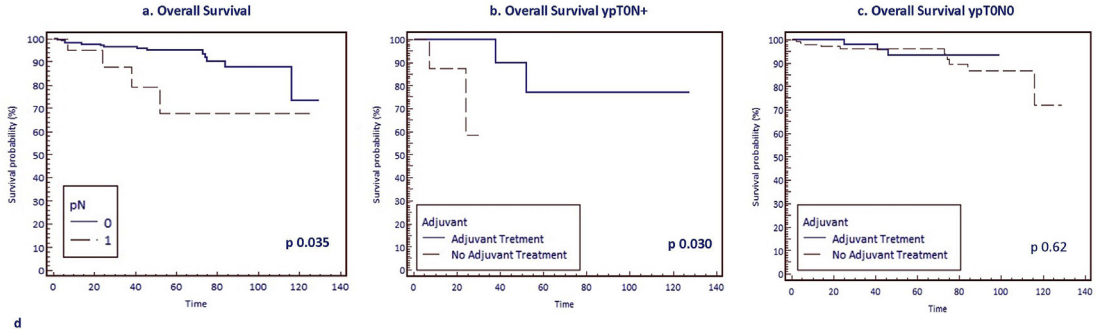


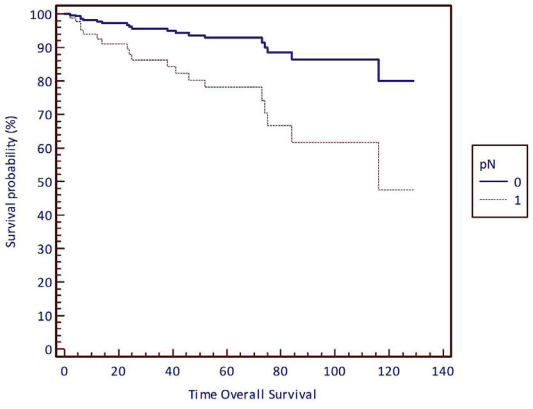

d

| variable | OS (log-rank test p value) | DFS (log-rank test p value) | DSS (log-rank test p value) |
|---|---|---|---|
| **Surgical Treatment LE *vs* TME** | 0.323 | 0.486 | 0.664 |
| **Stenosis Presence *vs* Absence** | 0.212 | 0.698 | 0.109 |
| **Tumor Location <5 cm *vs* >5 cm** | 0.075 | 0.227 | 0.134 |
| **Neo-adjuvant Treatment Short RT *vs* CHT-RT** | 0.236 | 0.471 | 0.882 |
| **pN (pN+ *vs* pN0)** | **0.035** | 0.19 | 0.07 |

Figure 2. **a.** Overall survival in ypT0 patients according with the nodal *status*; **b** Overall survival in ypT0N + patients according with the adjuvant treatment; **c.** Overall survival in ypT0N0 patients according with the adjuvant treatment and **d.** Results of the survival analysis according to the surgical strategy, presence of a clinical/endoscopic stenosis, tumor location and type of neo-adjuvant treatment performed, nodal pathological *status*.

alone).[10,26] In our study, NATs modalities did not impact patients outcomes in patients presenting a complete or nearly complete pathologic tumor response.

Currently, the optimal surgical approach in patients with CRC is still a matter of debate. Indeed, although a LE with organ preservation could be highly attractive, TME with at least 12 nodes harvested is still considered the standard practice. Nowadays LE has been reserved to highly selected patients within clinical trials, those refusing a major surgical procedure (i.e. low anterior resection, abdominal-perineal resection) or presenting severe co-morbidities.[28–30] ESMO guidelines recommend LE in case of pathological specimen consistent with a ypT0, exclusively in highly selected cases out of a clinical trial, followed by closed surveillance after the evaluation of the relapses risk on the bases of a nomogram.[10,31] Within this area of interest, prominent investigator groups are assessing the oncological efficacy of a watch and wait strategy in patients




**Cox proportional hazard regression analysis – stepwise model**

| End-point Overall Survival | | | | |
|---|---|---|---|---|
| Covariate | b | SE | P | Exp(b) |
| pN | 1.500 | 0.600 | 0.012 | 4.480 |

**Variables not included in the model: Tumor Location (> 5 cm *vs* < 5 cm); Stenosis (absence *vs* presence); Surgical approach (TME *vs* Local excision); Neo-adjuvant Treatment (Long Course CHT-RT *vs* Short Term RT); Adjuvant Treatment (performed *vs* not performed).**

Figure 3. Cox proportional-hazard regression model: N positive *vs* N0 curves results of the multivariate analysis.

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presenting a cCR, but results are ongoing and long-term results are still awaited.[32,33]

In our study 8.7% of the patients were N+ as in previous findings,[12,21] and the nodal positivity was a prognostic factor statistically correlated with OS. For these N+ patients a TME would be mandatory and therefore the identification of clinical, radiological and molecular features correlated with nodal positivity in the ypT0 sub-group (or conversely with the absence of nodal metastases) could significantly impact patients management, given that the surgical strategy was not correlated with patients survivals.

A very recent study by Bosh and co-authors[21] reviewed the histopathology of a pooled group of ypT0-2 rectal cancers with the objective of assessing the pattern of nodal positivity. The authors documented that a clinical nodal positivity, a high pathological grade and a residual tumor diameter >1 cm were independent predictors of nodal disease following CHT-RT. Also, data from the SEER Registry showed that the rate of ypN + patients within the ypT0 patients could be up to 13%, but the rate is much lower (3%) if the patient was assessed as clinical nodal negative on pre-treatment MRI.[34] Finally, with respect to nodal metastasis distribution, patients from the German trial CAO/ARO/AIO-04, where noted to have more nodal metastases in the peritumoral mesorectum (7.7%) than proximal to the tumor (1.5%), whereas no metastases were identified below the tumor level, and the peri-tumoral/proximal nodal involvement impacted disease specific survival.[35] In line with this, Park and co-workers[36] evaluated 406 ypT0-2 patients in relation to the nodal positivity and survival outcome. According to their results, local recurrences occurred more frequently in the ypN + *vs* ypN0 patients; authors concluded that the use of the ypT parameter to stratify patients for local excision and organ preservation might result in an under-treatment of a very high proportion of patients. Similarly, although conducted on a smaller cohort of 91 ypT0 patients, Jang and associates documented on multivariate analysis that ypN + *status* was a significant risk factor for recurrence.[37]

In a meta-analysis including 1263 pCR patients and 2100 non-pCR with a mean follow-up of 55 months, the weighted mean rate for distant metastases was 8.7% and for local recurrence was 0.7% in the pCR group, consistently with our results. Indeed, comparing with non-responders, a pCR was associated with significant fewer local recurrences (OR 0.2) and distant metastases (OR 0.2) and better OS (OR 3.28) and DFS (OR 4.33) after 5 years.[18] In this study, however, authors did not compare the survival of ypT0N0 *vs* ypT0N+. The same consideration regarding ypN + patients could be made for the pooled data analysis including 484 pCR published by Maas and co-authors in 2010.[15] Interestingly, the same author documented in 2015 that pCR patients did not show additional benefits from adjuvant chemotherapy with the endpoint of survivals.[16] Also, a first analysis of the EORTC trial published in 2007 displayed some advantages in the ypT0-2 subgroup for adjuvant CT (consistently with the idea that patients who respond seem to maintain the benefit also by the use of chemotherapy after surgery), but these benefits were not further documented after 10 years of follow-up.[7,27] In line with these concerns, the majority of the patients included in this study were not treated with adjuvant therapy following surgical resection, although a discrepancy was noted when compared N+ and N0 rectal cancers. Despite this current guidelines provided by NCCN suggest to perform chemotherapy following surgical resection independently from the pathological stage.[24]

Our results documented that ypT0N + patients had a significant OS benefit if treated with adjuvant CT. However, the same effect was not documented in ypT0N0 patients. Although this is a preliminary result, which needs to be confirmed on a larger sample, it stresses the necessity of a precise pre-operative diagnosis following NAT in order to tailor treatments. A previous research documented that NAT significantly impacts and reduces the LNH in the specimen, however the diagnosis of a persistence of nodal metastasis could be crucial: a very recent study proposed a cut-off of 2.5 mm at MRI post-NAT for nodal positivity.[38,39] Indeed, all the clinical, radiological or molecular assessments, which can predict the complete tumor regression should be mandatory in referral centres since could be highly effective for the decision making process of those patients. Undoubtedly, the 3 years survival analysis of patients treated according to the watch and wait protocol seem promising and oncologically safe in selected rectal cancers.[40] On this basis, and according to our results, we developed a proposal for ypT0 and ycT0 management, Supplement Figure.

Accordingly, if a rectal cancer is assessed ycT0 following NAT with a high negative predictive value, emphasis should be given on the nodal *status*. ycT0N0 could be selected for a LE/wait and watch protocol in selected cases,[40] whereas ycT0N + should be treated with a TME. Following resection, if the pathological report is consistent with ypT0N0 the patient could be scheduled for follow-up, whereas ypT0N + or ypT + any N should be treated with adjuvant CT. Follow-up of these patients should always investigate lungs, since a great percentage of distal metastases were diagnosed at the lung site.

Limits of this study could be ascribed to the retrospective design with a long time period enrollment and the sub-optimal power of the survival analysis (post-hoc two tails 1-β 0.54) given by the small sample of N+ patients. On the other hand, this study results from the multi-institutional commitment of high volume referral centres for CRC treatment with a long mean follow-up. Accordingly, and on the bases of the proportions-survival rates here observed, a larger European study including multiple Institutions aiming to recruit 1000 patients would provide an optimal and powered analysis. Notably surgical strategies (LE *vs* TME) did not impact ypT0 outcomes, suggesting that also a LE may be a safe option for those ypT0N0 patients whose standard of care indication is TME.

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## Conclusion

Nodal positivity accounts for the 8.7% of the rectal cancers presenting a complete or nearly complete response after neo-adjuvant treatment and was the only independent variable correlated with patients' OS. Recurrences were mostly diagnosed at a distant site and within the third year of follow-up. Although current international guidelines still recommend the use of adjuvant CT, the majority of the patients did not perform adjuvant treatment following surgery. Our results documented that adjuvant CT significantly impacts the OS of ypT0N + patients. The validation of this study in a larger setting thus could be crucial and open to new frontiers for CRC patients' management.

## Conflict of interest

None of the authors has any potential financial conflict of interest related to this manuscript.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2017.04.017.

## References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;**49**:1374–403.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;**66**:7–30.
3. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;**12**:575–82.
4. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;**93**:1215–23.
5. Gerard JP, Conroy T, Bonnetain F, 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**:4620–5.
6. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**:1926–33.
7. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;**15**:184–90.
8. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;**1**:1479–82.
9. Kapiteijn E, Putter H, van de Velde CJ. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002;**89**:1142–9.
10. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol* 2012;**23**:2479–516.
11. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus non operative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;**240**:711–7.
12. Al-Sukhni E, Attwood K, Mattson DM, et al. Predictors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Ann Surg Oncol* 2016;**23**:1177–86.
13. Faivre-Finn C, Benhamiche AM, Maingon P, et al. Changes in the practice of adjuvant radiotherapy in resectable rectal cancer within a French well-defined population. *Radiother Oncol* 2000;**57**:137–42.
14. Capirci C, Valentini V, Cionini L, 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**:99–107.
15. Maas M, Nelemans PJ, Valentini V, 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* 2010;**11**:835–44.
16. Maas M, Nelemans PJ, Valentini V, et al. Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection: a pooled analysis of 3,313 patients. *Int J Cancer* 2015;**137**:212–20.
17. 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.
18. 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**:918–28.
19. Ryan JE, Warrier SK, Lynch AC, et al. Assessing pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Colorectal Dis* 2015;**17**:849–61.
20. Ryan JE, Warrier SK, Lynch AC, et al. Predicting pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a systematic review. *Colorectal Dis* 2016;**18**:234–46.
21. Bosch SL, Vermeer TA, West NP, et al. Clinicopathological characteristics predict lymph node metastases in ypT0-2 rectal cancer after chemoradiotherapy. *Histopathology* 2016 Jun 6. http://dx.doi.org/10.1111/his.13008.
22. Cotte E, Passot G, Decullier E, et al. 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**:544–53.
23. http://www.oncoguida.it/html//home.asp.
24. *NCCN clinical practice guidelines in Oncology (NCCN Guidelines®) version 2*; 2016. 04.06.2016. www.nccn.org.
25. Rega D, Pecori B, Scala D, et al. Evaluation of tumor response after short-course radiotherapy and delayed surgery for rectal cancer. *Plos One* 2016;**11**:e01160732.
26. Ceelen W, Fierens K, Van Nieuwenhove Y. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a systematic review and meta-analysis. *Int J Cancer* 2009;**124**:2966–72.
27. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**355**:1114–23.
28. Bonnen M, Crane C, Vauthey JN, et al. Long-term results using local excision after preoperative chemoradiation among selected T3 rectal cancer patients. *Int J Radiat Oncol Biol Phys* 2004;**60**:1098–105.
29. Perez RO, Habr-Gama A, Lynn PB, et al. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. *Dis Colon Rectum* 2013;**56**:6–13.
30. Pucciarelli S, De Paoli A, Guerrieri M, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. *Dis Colon Rectum* 2013;**56**:1349–56.
31. Valentini V, van Stiphout RG, Lammering G, 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**:3163–72.

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32. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the onCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016;**17**:174–83.
33. Beets GL, Figueiredo NL, Habr-Gama A, et al. A new paradigm for rectal cancer: organ preservation: introducing the International Watch & Wait Database (IWWD). *Eur J Surg Oncol* 2015;**41**:1562–4.
34. Wan J, Liu K, Zhu J, et al. Implications for selecting local excision in locally advanced rectal cancer after preoperative chemoradiation. *Oncotarget* 2015;**6**:11714–22.
35. Sprenger T, Rothe H, Becker H, et al. Lymph node metastases in rectal cancer after preoperative radiochemotherapy: impact of intramesorectal distribution and residual micrometastatic involvement. *Am J Surg Pathol* 2013;**37**:1283–9.
36. Park IJ, You YN, Skibber JM, et al. Comparative analysis of lymph node metastases in patients with ypT0-2 rectal cancers after neoadjuvant chemoradiotherapy. *Dis Colon Rectum* 2013;**56**:135–41.
37. Jang TY, Yu CS, Yoon YS, et al. Oncologic outcome after preoperative chemoradiotherapy in patients with pathologic T0 (ypT0) rectal cancer. *Dis Colon Rectum* 2012;**55**:1024–31.
38. La Torre M, Mazzuca F, Ferri M, et al. The importance of lymph node retrieval and lymph node ratio following preoperative chemoradiation of rectal cancer. *Color Dis* 2013;**15**:e382–388.
39. Heijnen LA, Maas M, Beets-Tan RG, et al. Nodal staging in rectal cancer: why is restaging after chemoradiation more accurate than primary nodal staging? *Int J Colorectal Dis* 2016;**31**:1157–62.
40. Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst* 2016;**108**. http://dx.doi.org/10.1093/jnci/djw171 pii:djw171.

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