Pathologic Complete Response (pCR) To Neoadjuvant Chemoradiation (CRT) Of uT2N0 Rectal Cancer (RC) Treated By Local Excision (LE): Results Of The ACOSOG Z6041 Trial

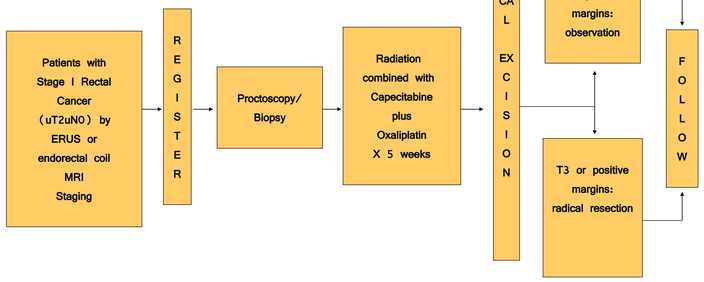
Julio Garcia-Aguilar[1], Qian Shi[2], Charles R. Thomas, Jr.[3], Emily Chan[4], Peter Cataldo[5], Jorge Marcet[6], David Medich[7], Alessio Pigazzi[1], Samuel Oommen[8], Mitchell C. Posner[9], ACOSOG

City of Hope National Medical Center, Duarte, Duarte, CA[1]; Division of Biomedical Statistics and Informatics, Mayo Clinic Rochester, MN[2]; Knight Cancer Institute, Oregon Health and Science University, Portland, OR[3]; Vanderbilt University Medical Center, Nashville, TN[4]; University of Vermont, Burlington, VT[5]; Tampa General Hospital, Tampa FL[6]; Allegheny Cancer Center, Pittsburgh, PA[7]; John Muir Hospital, Walnut Creek, CA[8]; University of Chicago Medical Center, Chicago IL[9].

1 BACKGROUND

Early rectal cancer treated with total mesorectal excision (TME) benefits from high cure rates and low recurrence rates. However, TME is associated with significant mortality (1-6%) and morbidity. Local excision (LE) is an alternative to TME with lower morbidity and mortality. LE alone results in a high rate of local recurrence. Chemoradiation (CRT) after or before LE may lower the recurrence rate. To investigate this the American College of Surgeons Oncology Group (ACOSOG) designed a single-arm, non-randomized, multi-center Phase II clinical trial using neoadjuvant CRT followed by LE in patients with ultrasound-staged T2N0 rectal cancer (Z6041 trial). Here, we report preliminary findings from this trial, describing the pathologic complete response (pCR) rate.

2 STUDY DESIGN



3 PATIENTS AND METHODS

Prior to enrollment patients underwent complete colonoscopy, rigid proctoscopy, endorectal ultrasound (ERUS) or endorectal coil MRI, abdominal and pelvic CT, and chest x-ray or chest CT. Central review of all staging ERUS or endorectal coil MRI images was performed for quality assurance.

Patients had an ECOG PS of ≤ 2 and had histologically confirmed invasive rectal adenocarcinoma with the distal tumor margin located within 8 cm of the anal verge. TN stage was T2N0 in all cases, established by ERUS or endorectal coil MRI. Greatest tumor diameter was ≤ 4 cm. Patients with tumors fixed to adjacent structures on digital rectal examination were not eligible.

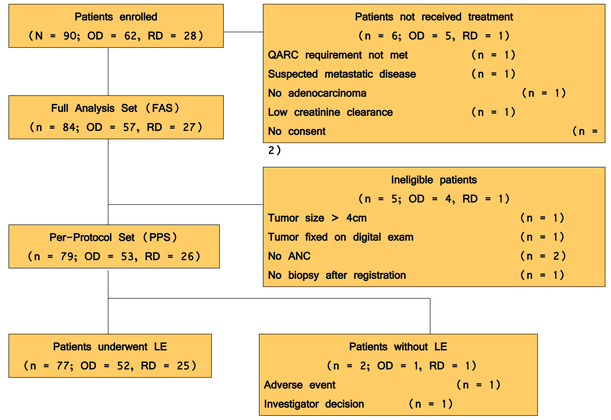
Patients were treated with capecitabine (825 mg/m^2 days 1-14 and 22-35) and oxaliplatin (50 mg/m^2 weeks 1, 2, 4 and 5) during radiation (RT) (total dose 54 Gy) (Original dose, OD group). Due to toxicity, the dose of RT was reduced to 50.4 Gy and capecitabine to 725 mg/m^2 (5 days/week/5 weeks) (Revised dose, RD group) [shown in 5].

LE was performed approximately 4-8 weeks after completing neoadjuvant CRT, using either a conventional transanal approach or a transanal endoscopic microsurgery method. After LE tumors were staged according to AJCC criteria.

Secondary study endpoints include pathologic complete response (pCR) rate of primary tumor to neoadjuvant CRT, surgeon sensitivity and specificity of pCR prediction prior to surgery, resectability rate with respect to negative margins, adverse events (AEs) relating to CRT and postoperative complications (PCs). Note that AEs and PCs are not presented here.

Primary study endpoint: rate of disease-free survival (DFS) 3 years after LE. To date, all patients have finished treatment and the pathological data are complete and currently maturing.

4 PATIENT DISPOSITION



5 TREATMENT REGIMEN

CRT	Overall n = 84	OD group n = 57	RD group n = 27
Capecitabine total dose ($\times 10^2$ mg) median (range)	7.5 (3, 14)	8.4 (5, 14)	6.3 (3, 9)
Oxaliplatin total dose ($\times 10^2$ mg) median (range)	3.8 (0, 5)	3.8 (2, 5)	3.8 (0, 5)
Radiotherapy total dose (Gy) median (range)	54 (18, 59)	54 (18, 59)	50.4 (50, 55)

62 (72%) patients completed CRT per study protocol. More patients completed radiotherapy per protocol (74 patients, 88%) than chemotherapy (68 patients, 81%). The time from beginning and end of CRT to surgery was not different between dosage groups.

6 PATIENT AND PRE-TREATMENT TUMOR CHARACTERISTICS

Demographic or Disease Characteristic	Overall n = 84	OD group n = 57	RD group n = 27
	n (%)	n (%)	n (%)
Age, years Median (range)	63 (30 - 83)	63 (30 - 80)	64 (45 - 83)
Male	55 (66)	35 (61)	20 (74)
Race, White	77 (92)	51 (90)	26 (96)
ECOG PS 0	70 (83)	49 (86)	21 (78)
Tumor Size, cm Mean ± sd	2.9 ± 0.8	2.8 ± 0.8	2.9 ± 0.7
Distance from Anal Verge, cm Mean ± sd	5.1 ± 2.0	4.9 ± 1.9	5.4 ± 2.1

7 POST-TREATMENT PATHOLOGIC TUMOR CHARACTERISTICS

Patients that underwent LE	Overall n = 77	OD group n = 52	RD group n = 25
	n (%)	n (%)	n (%)
Pathologic tumor size, cm mean ± sd	0.9 ± 1.1	0.9 ± 1.1	0.9 ± 1.1
Tumor T stage			
T0	34 (44)	25 (48)	9 (36)
Tis	5 (7)	3 (6)	2 (8)
T1	10 (13)	7 (14)	3 (12)
T2	23 (30)	14 (27)	9 (36)
T3	4 (5)	2 (4)	2 (8)
*Tx	1 (1)	1 (2)	0 (0)
Negative resected margins	76 (99)	52 (100)	24 (96)

5 LE specimens contained lymph nodes; one with a T3 tumor had a positive node.

8 PATHOLOGIC COMPLETE RESPONSE (pCR)

All eligible patients that completed CRT, irrespective of whether or not that had LE, were evaluated for pathologic complete response (pCR) rate of the primary tumor to the neoadjuvant CRT regimen.

pCR was defined as complete absence of dysplastic cells from the bowel wall and mesorectal lymph nodes included in the surgical specimen, ypT0N0.

Overall 34 out of 79 patients (43%) had a pCR; 25 (47%) in the original dose group and 9 (35%) in the revised dose group.

No pre-treatment tumor characteristic or treatment variable associated with pCR.

A complete clinical response (cCR) was concordant with pCR in 29 out of 34 patients; sensitivity 85%, specificity 67%, positive prediction rate 69%, negative prediction rate, 86%.

9 CONCLUSIONS

Concomitant pelvic radiotherapy plus capecitabine and oxaliplatin-based CRT followed by LE for T2N0 rectal cancer results in a pCR in almost half the treated patients.

The pCR is higher than that reported for Stage II and III tumors and this regimen results in one of the highest pCR rates observed in a co-operative group trial for early stage rectal cancer.

Nearly all eligible patients that received per protocol CRT underwent LE with negative margins.

The ability of surgeons to predict a pCR was higher than previously reported.

This project is supported by the ACOSOG grant no. NCI U10 CA076001; Sanofi-Aventis.

ACOSOG
American College Of Surgeons Oncology Group

www.acosog.org