Clinical impact of mucinous and poorly differentiated tumors on the outcome of patients with stage II colon cancer: a TOSCA subgroup analysis

G. ROSATI,[1*] F. GALLI,[2] M. CANTORE,[3] S. LONARDI,[4] M. BANZI,[5] M.G. ZAMPINO,[6] R. MATTIOLI,[7] N. PELLA,[8] M. RONZONI,[9] M. DI BARTOLOMEO,[10] S. TAMBERI,[11] P. MARCHETTI,[12] S. BOZZARELLI,[13] D. CORSI,[14] A. M. BOCHICCHIO,[15] F. ARTIOLI,[16] R. LABIANCA,[17] F. GALLI,[2] D. BILANCIA,[1] G. BREGNI,[18] ON BEHALF OF TOSCA (THREE OR SIX COLON ADJUVANT) INVESTIGATORS

[1]OSPEDALE S. CARLO, POTENZA; [2]ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS, MILANO; [3]AZIENDA USL 1 DI MASSA E CARRARA – CARRARA; [4]IRCCS ISTITUTO ONCOLOGICO VENETO, PADOVA; [5]AZIENDA USL-IRCCS, REGGIO EMILIA; [6]IRCCS ISTITUTO EUROPEO DI ONCOLOGIA, MILANO; [7]AZIENDA OSPEDALIERA MARCHE NORD, PESARO/FANO; [8]AZIENDA OSPEDALIERA UNIVERSITARIA S. MARIA DELLA MISERICORDIA, UDINE; [9]OSPEDALE SAN RAFFAELE, MILANO; [10]FONDAZIONE IRCCS INT, MILANO; [11]OSPEDALE DEGLI INFERMI, FAENZA; [12]OSPEDALE SANT'ANDREA, UNIVERSITÀ SAPIENZA, ROMA E IRCCS ISTITUTO DERMOPATICO DELL'IMMACOLATA, ROMA; [13]ISTITUTO CLINICO HUMANITAS IRCCS, ROZZANO; [14]OSPEDALE S. GIOVANNI CALIBITA FATEBENEFRATELLI, ROMA; [15]OSPEDALE ONCOLOGICO REGIONALE CROB, RIONERO IN VULTURE; [16]OSPEDALE B. RAMAZZINI, CARPI; [17]CANCER CENTER ASST PAPA GIOVANNI XXIII, BERGAMO; [18]IRCCS SAN MARTINO-IST, GENOVA, ITALY

Background

ASCO and ESMO guidelines have identified inadequate sampling of lymph nodes, pT4 primary tumors, obstruction or perforation, lymphovascular and perineural invasion, and poorly differentiated tumors as negative prognostic factors supporting the clinicians in treating their patients with stage II colon cancer (CC). However, the influence of histological subtypes on the risk of death or disease recurrence remains controversial.

Two large retrospective studies including thousands of patients recently demonstrated that mucinous adenocarcinoma (MUC) is associated with a worse prognosis.

The Three or Six Colon Adjuvant (TOSCA) trial is an Italian phase III, multicenter noninferiority trial in which randomized patients with high-risk stage II or stage III CC received 3 or 6 months of adjuvant fluoropyrimidine-oxaliplatin chemotherapy. This study failed to demonstrate the noninferiority of 3 months versus 6 months of treatment, and the hazard ratio (HR) for relapse-free survival (RFS) in stage II was higher than that observed in stage III favoring the 6 months of treatment.

Methods

TOSCA trial compared 3 versus 6 months of fluoropyrimidine-oxaliplatin adjuvant chemotherapy in 3,759 patients with high-risk stage II or stage III CC. We investigated whether the histological subtype [(MUC) or non-mucinous adenocarcinoma (NMUC)] had an impact on the effect of treatment duration in terms of RFS and OS in the subgroup of patients with high-risk stage II, grade 3 CC, enrolled in the TOSCA trial.

RFS was defined as the time between randomization and disease relapse or death from any cause. Patients who did not relapse or die during the study were censored at the date of the last disease assessment. OS was defined as the time interval between randomization and death from any cause. Patients who did not die during the study were censored at the date they were last known to be alive.

Results

Out of 3,614 patients enrolled in the per-protocol population defined in the TOSCA trial, 85 MUC and 389 NMUC patients were included in this analysis.

A significant interaction between treatment duration and histology was observed. Figure 1 summarized the efficacy results on RFS and OS of the impact of treatment duration in the two histological subgroups.

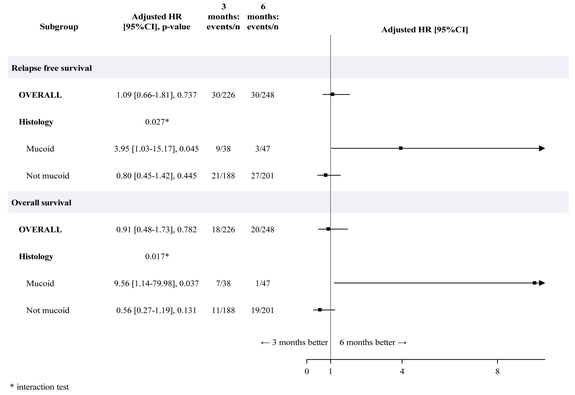
In the subgroup of patients with MUC, worse RFS (adjusted HR 3.95; 95% CI 1.03–15.17; p = 0.045) and OS (HR, 9.56; 95% CI, 1.14–79.98; p = 0.037) were detected for patients treated in the 3 month arm.

No statistically significant differences between treatment arms were detected in the subgroup of patients with NMUC.

RFS and OS Kaplan Meier curves are provided in Figure 2 for the subgroup of patients with MUC and in Figure 3 for the subgroup of patients with NMUC.

Differences between treatment duration were detected in the MUC group in both RFS (p = 0.027) and OS (p = 0.017), whereas no differences were highlighted in the group of patients with NMUC.

Figure 1



* interaction test

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Figure 2

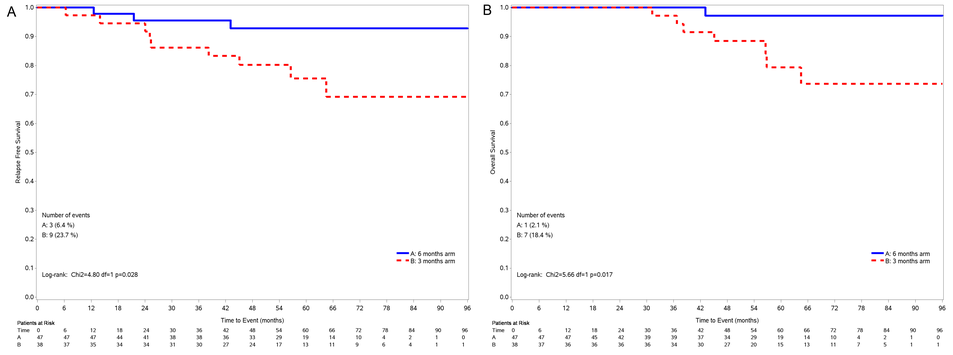
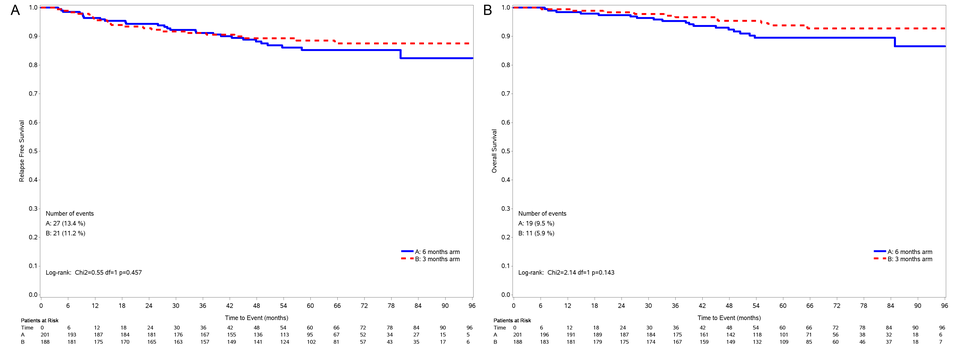


Figure 3



Conclusions

Our study has several limitations related to the imbalance in the number of patients between the two groups as well as to the low sample size that results in a limited statistical power.

Strengths consist in its prospective enrolment and in its innovative purpose, since for the first time a study has explored the predictive role of the histological subtype on the effect of chemotherapy in poorly differentiated, stage II CC patients.

Our results suggest that the evaluation of MUC histology could be considered a relevant factor for identifying stage II CC patients who need longer chemotherapy treatment.

Nevertheless, we need larger prospective studies to confirm the role of MUC as a predictive factor in our population and to assess the combined use of histology and other prognostic/predictive factors already implemented in the guidelines that define the administration of chemotherapy in stage II CC patients.

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*Corresponding author email address: oncogerry@yahoo.it

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