Khorana score and thromboembolic risk in stage II–III colorectal cancer patients: a post hoc analysis from the adjuvant TOSCA trial

Sandro Barni, Gerardo Rosati, Sara Lonardi, Nicoletta Pella, Maria Banzi, Maria G. Zampino, Katia F. Dotti, Lorenza Rimassa, Paolo Marchetti, Evaristo Maiello, Fabrizio Artioli, Daris Ferrari, Roberto Labianca, Paolo Bidoli, Alberto Zaniboni, Alberto Sobrero, Vincenzo Iaffaioli, Sabino De Placido, Gian Luca Frassineti, Andrea Ciарlo, Angela Buonadonna, Nicola Silvestris, Elena Piazza, Lorenzo Pavesi, Mauro Moroni, Mario Clerico, Massimo Aglietta, Paolo Giordani, Francesca Galli, Fabio Galli and Fausto Petrelli, On behalf of TOSCA Investigators

Abstract

Background: The risk of venous thromboembolic events (VTE) during adjuvant chemotherapy for colorectal cancer (CRC) is unknown. We aim to evaluate if the Khorana score (KS) can predict this risk, and if it represents a prognostic factor for overall survival (OS) through a post hoc analysis of the phase III TOSCA trial of different durations (3- versus 6-months) of adjuvant chemotherapy.

Methods: A logistic regression model was used to test the associations between the risk of VTE and the KS. The results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). To assess the effect of the KS on OS, multivariable analyses using Cox regression models were performed. The results are expressed as hazard ratios (HR) with 95% CI.

Results: Among 1380 CRC patients with available data, the VTE risk (n = 72 events: 5.2%) was similar in the two duration arms (5.5% versus 4.9%), with 0.2% of patients belonging to the high-risk KS group. Rates of VTE were similar in the low- and intermediate-risk groups (4.8% versus 6.4%). KS did not represent an independent predictive factor for VTE occurrence. Chemotherapy duration was not associated with VTE risk. In addition, KS was not prognostic for OS in multivariate analysis (HR: 0.92, 95% CI, 0.63–1.36; p = 0.6835).

Conclusions: The use of the KS did not predict VTEs in a low–moderate thromboembolic risk population as CRC. These data did not support the use of KS to predict VTE during adjuvant chemotherapy, and suggest that other risk assessment models should be researched.

Keywords: adjuvant chemotherapy, colorectal cancer, Khorana score, thrombosis

Introduction

Venous thromboembolic events (VTE), which comprise deep vein thrombosis and pulmonary embolism, are a frequent complication in patients with cancer, and are associated with increased morbidity and mortality.1 Among the VTE assessment models, the Khorana risk score, developed by Khorana, is the best-validated model with which to stratify VTE risk in ambulatory patients with cancer.2 The Khorana score (KS) predicts thrombosis risk based on a collection of simple variables, including type of cancer, body mass index (BMI), and complete blood count (platelet, leukocyte, hemoglobin). Cancer patients with a KS of 3 or greater are at high risk for developing blood clots. However, KS applies to ambulatory cancer patients with metastatic disease and was never validated in an adjuvant setting.

Among solid tumors, colorectal cancer (CRC) is associated with lower risk (fourfold lower) compared with stomach and pancreatic cancers.2 Little...
is known about the risk of VTEs and prognostic classification in early (stages I–III) CRC. In a retrospective series of gastrointestinal cancers, the incidence of VTEs among 1299 CRC patients was 8.9% (115 cases). The 25% (29 cases) of VTEs occurred in patients with localized disease, with a median time to occurrence of 7.1 months, and with 94% of VTEs developing in patients with a low or intermediate Khorana risk score. In a prospective study by Mandala and colleagues, the rate of VTE across 122 colon cancer patients receiving adjuvant fluorouracil was 7.4%, with a basal prechemotherapy platelet count and a previous episode of VTE that were independently associated with the risk of VTE during adjuvant chemotherapy.

VTE is associated with significant resource utilization and increased healthcare costs in ambulatory cancer patients. In particular, in the postoperative setting, where adjuvant chemotherapy is potentially curative, the selection of high-risk patients with the aim of preventing vascular events and possibly reducing mortality is of relevant importance. A complementary study to the TOSCA trial was planned to investigate the discriminatory power of Khorana score in terms of occurrence of VTE, time to VTE, and overall survival (OS).

Material and methods

Study design and data extraction

Patients included in the present post hoc analysis are a subgroup of those enrolled in TOSCA trial. Participation was not mandatory, but at the discretion of each center. Inclusion of patients followed this approach: all centers that enrolled at least 10 patients in the TOSCA trial were given the opportunity to participate in this study. To avoid selection bias, the centers that decided to participate were asked to include at least 10 consecutive patients.

Data on baseline information (cancer stage and histopathology, age, gender, current medications, recent surgery, Eastern Cooperative Oncology Group performance status (ECOG-PS), chemotherapy regimen) were collected prospectively during the main study. Data on BMI, number of leukocytes, platelets, and hemoglobin were recorded retrospectively, and the KS was calculated accordingly. Both asymptomatic and symptomatic VTE were recorded. Symptomatic thrombosis forms were checked with standard diagnostic methods. The medical charts and radiological history of all patients were checked for ultrasonography of the limbs, chest, and abdominal computed tomography scan, and perfusion/ventilation lung scan. VTEs were diagnosed by the treating clinician on the basis of clinical suspicion, using the usual diagnostic procedures or with the per protocol radiologic examinations, and were treated as for standard of care. Approval was obtained from local ethics committee for each participating site. The TOSCA trial followed the guiding principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization, and all patients provided written informed consent.

TOSCA trial overview

Briefly, the TOSCA study is a phase III, randomized, open-label, non-inferiority, multicenter trial conducted in 130 Italian centers and involving patients with resected colon cancer located >12 cm from the anal verge by endoscopy, or above the peritoneal reflection at surgery. After stratification by center and stage (high-risk stage II versus stage III), patients between 3 and 10 weeks from surgery were assigned randomly in a 1:1 ratio to receive 3 months of FOLFOX-4/XELOX (experimental group) or 6 months of FOLFOX-4/XELOX (control group). The primary end point was relapse-free survival (RFS), defined as the time from the date of randomization up to the date of the first relapse or death from any cause. At the primary analysis, the trial failed to formally show non-inferiority of 6 months of treatment to the predefined margin of 20% relative increase. However, in the low risk population (pN1 disease), the 3 months was similar to the 6-months duration in term of RFS.

Statistical analysis

Continuous variable summaries included mean and standard deviation (SD), median and first (Q1), third (Q3) quartile and range, whereas, for categorical variables, the frequency and percentage of subjects who were in the particular group were used; the denominator for the percentage calculation was based on the total number of subjects in the relevant analysis group. Chi-square test (or Fisher exact test, as appropriate) and t test were used to compare categorical and continuous variable, respectively. The proportion of patients who experienced a VTE were provided for each KS risk group. Since the TOSCA trial randomized patients to two regimen durations, the proportion of events was calculated also for each TOSCA arm, and the proportion of patients with a VTE in the first 3 months of treatment were extracted.

Therapeutic Advances in Medical Oncology 12
To test the associations between the risk of VTE and the KS, treatment duration, and clinical characteristics on outcomes and logistic regression models were used. The results are expressed as odds ratio (OR) with its 95% confidence interval (95% CI). Finally, the sensitivity, sensibility, positive and negative predictive value, and accuracy of the KS were calculated and provided. Time to VTE was defined as the time from the date of randomization to the date of the first VTE. Deaths without a previous occurrence of a VTE were considered as competing events. OS was defined as the time from the date of registration to the date of death from any cause. Subjects who were not reported as having died at the time of the analysis were censored at the date they were last known to be alive. Fine–Gray and Cox regression models were used to assess the effect of the KS, treatment duration, and demographic and clinical characteristics on time to VTE and OS, respectively. The results are expressed as subdistribution hazard ratio (SHR) or hazard ratio (HR) with their 95% CI.

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) at the Istituto di Ricerche Farmacologiche Mario Negri IRCCS.

**Results**

Of the 3759 patients randomized in the TOSCA trial, 1713 were included in this complementary study, and 1383 were assessable for the analyses (Figure 1). Since only three patients were classified as high risk according to KS, they were excluded from analyses. Therefore, 1380 patients were included in this analysis.
Overall, 1053 (76.4%) and 327 (23.6%) patients were classified as low and intermediate risk, respectively. The two groups were well balanced for demographic and pathological features, except for sex, with more female patients in the low risk group (Tables 1 and 2). Almost all patients had an adenocarcinoma (99.1%), and most of them were stage III (65.5%); only 4.4% of patients had a PS ECOG of 1. In both groups, FOLFOX and XELOX were equally prescribed. Median follow up was similar (62 months) in the low- and intermediate-risk groups. Overall, the characteristics of

### Table 1. Demographic and clinical characteristics.

|                | Low risk  | Intermediate risk | Overall | t test or Chi-square test p value |
|----------------|-----------|-------------------|---------|---------------------------------|
|                | n = 1053  | n = 327           | n = 1380|                                 |
| Age            |           |                   |         | 0.2620                          |
| Mean [SD]      | 62.6 [9.9]| 61.9 [9.7]        | 62.4 [9.8]|                                |
| Median [Q1–Q3]| 63.9 [56.9–70.0]| 63.3 [56.1–69.0]| 63.6 [56.8–69.7]|                         |
| Min–Max        | 21.0–82.0| 27.7–79.3         | 21.0–82.0|                                |
| Female sex, n [%] | 455 (43.8)  | 193 (56.6)       | 648 (47.0)| 0.0001                          |
| Performance status, n [%] |               |                   |         | 0.0438                          |
| 0              | 1013 [96.2] | 306 [93.6]       | 1319 [95.6]|                                |
| 1              | 40 [3.8]   | 21 [6.4]          | 61 [4.4] |                                |
| Tumor site     |           |                   |         | 0.6393                          |
| Single site    | 1014 [96.4]| 316 [96.9]       | 1330 [96.5]|                                |
| Multiple site  | 38 [3.6]   | 10 [3.1]          | 48 [3.5] |                                |
| Missing        | 1          | 1                 | 2       |                                |
| Single site specification, n [%] |               |                   |         | 0.1717                          |
| Ascending colon| 292 [28.8] | 104 [32.9]       | 396 [29.8]|                                |
| Hepatic flexure| 36 [3.6]   | 11 [3.5]         | 47 [3.5] |                                |
| Transverse colon| 54 [5.3]  | 25 [7.9]         | 79 [5.9] |                                |
| Splenic flexure| 35 [3.5]   | 12 [3.8]         | 47 [3.5] |                                |
| Descending colon| 172 [17.0]| 59 [18.7]       | 231 [17.4]|                                |
| Sigmoid colon  | 270 [26.7] | 67 [21.2]        | 337 [25.4]|                                |
| Sigmoid-rectum colon | 154 [15.2]| 38 [12.0]    | 192 [14.4]|                                |
| Missing        | 40         | 1                 | 51      |                                |
| Tumor site, n [%] |           |                   |         | 0.1038                          |
| Right sides    | 383 [36.4] | 140 [42.9]     | 523 [38.0]|                                |
| Left sides     | 625 [59.5] | 175 [53.7]     | 800 [58.1]|                                |
| Multiple site  | 43 [4.1]   | 11 [3.4]         | 54 [3.9] |                                |
| Missing        | 2          | 1                 | 3       |                                |

SD, standard deviation; Q1, first quartile; Q3, third quartile.
Table 2. Tumor characteristics.

|                      | Low risk n = 1039 | Intermediate risk n = 341 | Overall n = 1380 | t test or Chi-square test p value |
|----------------------|-------------------|--------------------------|-----------------|----------------------------------|
| **Histology - n (%)**|                   |                          |                 |                                  |
| Adenocarcinoma       | 956 (92.1)        | 305 (89.4)               | 1261 (91.4)     | 0.0991a                          |
| Mucoid adenocarcinoma| 75 (7.2)          | 31 (9.1)                 | 106 (7.7)       |                                  |
| Ring cell carcinoma  | 4 (0.4)           | 1 (0.3)                  | 5 (0.4)         |                                  |
| Adenosquamous carcinoma| 1 (0.1)        | 0 (0.0)                  | 1 (0.1)         |                                  |
| Other                | 2 (0.2)           | 4 (1.2)                  | 6 (0.4)         |                                  |
| Missing              | 1                 | 0                        | 1               |                                  |
| **Histology categorization, n (%)** |                   |                          |                 | 0.2009                           |
| Adenocarcinoma       | 956 (92.1)        | 305 (89.4)               | 1261 (91.4)     |                                  |
| Mucoid adenocarcinoma| 75 (7.2)          | 31 (9.1)                 | 106 (7.7)       |                                  |
| Other                | 7 (0.7)           | 5 (1.5)                  | 12 (0.9)        |                                  |
| Missing              | 1                 | 0                        | 1               |                                  |
| **T stage, n (%)**   |                   |                          |                 | 0.7043a                          |
| Tx                   | 7 (0.7)           | 0 (0.0)                  | 7 (0.5)         |                                  |
| T0                   | 1 (0.1)           | 0 (0.0)                  | 1 (0.1)         |                                  |
| T1                   | 24 (2.3)          | 7 (2.1)                  | 31 (2.3)        |                                  |
| T2a                  | 52 (5.0)          | 18 (5.3)                 | 70 (5.1)        |                                  |
| T2b                  | 32 (3.1)          | 8 (2.4)                  | 40 (2.9)        |                                  |
| T3                   | 772 (74.7)        | 251 (73.8)               | 1023 (74.5)     |                                  |
| T4                   | 145 (14.0)        | 56 (16.5)                | 201 (14.6)      |                                  |
| Missing              | 6                 | 1                        | 7               |                                  |
| **N stage, n (%)**   |                   |                          |                 | 0.1868a                          |
| Nx                   | 0 (0.0)           | 1 (0.3)                  | 1 (0.1)         |                                  |
| N0                   | 341 (33.0)        | 126 (37.1)               | 467 (34.0)      |                                  |
| N1                   | 520 (50.4)        | 162 (47.6)               | 682 (49.7)      |                                  |
| N2                   | 171 (16.6)        | 51 (15.0)                | 222 (16.2)      |                                  |
| Missing              | 7                 | 1                        | 8               |                                  |
| **Clinical stage, n (%)** |                 |                          |                 | 0.2181                           |
| II                   | 349 (33.6)        | 127 (37.2)               | 476 (34.5)      |                                  |
| III                  | 690 (66.4)        | 214 (62.8)               | 904 (65.5)      |                                  |

(Continued)
included patients were similar to the whole TOSCA population.

**Khorana score**
The parameter used for calculation of the KS are summarized in Table 3. One point each was attributed to number of platelets >350,000/mm³, Hb level <10 g/dL, leucocyte >11,000/mm³, BMI >35 (0 points were provided to all patients for disease site according to KS definition).

**VTE and KS prediction**
A total of 50 (4.8%) and 22 (6.4%) patients experienced at least one VTE in the low and intermediate KS groups, respectively (Table 4). Out of 72 total VTEs, 46 (63.8%) were symptomatic, 24 (33.3%) were asymptomatic (for 4 events this information was unknown). No differences were observed in terms of proportion of patients with a VTE between TOSCA arms. Moreover, 29 (40.8%) patients experienced a VTE in the first 3 months of treatment.

Univariate and multivariable analyses of the risk of thromboembolic events are presented in Table 5. The intermediate risk according to KS was not demonstrated to be associated with a higher risk of VTE [unadjusted OR (intermediate versus low risk): 1.35, 95% CI 0.80–2.28; \( p = 0.2633 \)] or with a shorter time to VTE [unadjusted SHR (intermediate versus low risk): 1.37, 95% CI 0.82–2.27; \( p = 0.2266 \)].

The sensitivity and the specificity of the KS were 29.2% and 76.6%, respectively. Moreover, the positive predictive value was equal to 6.4%, and the negative predictive value was equal to 95.2%; that is, 6.4% of patients at intermediate risk experienced a VTE, and 95.2% of patients at low

### Table 2. (Continued)

| Clinical stage subgroups, n (%) | Low risk \( n=1039 \) | Intermediate risk \( n=341 \) | Overall \( n=1380 \) | \( t \) test or Chi-square test \( p \) value |
|-------------------------------|----------------------|-------------------------------|--------------------|-----------------|
| II                            | 349 [33.7]           | 127 [37.5]                    | 476 [34.6]         | 0.4101          |
| III low risk                  | 474 [45.8]           | 143 [42.2]                    | 617 [44.9]         |                 |
| III high risk                 | 213 [20.6]           | 69 [20.4]                     | 282 [20.5]         |                 |
| Missing                       | 3                    | 2                              | 5                  |                 |
| Grade, n [%]                  |                      |                               |                    | 0.8757\(^a\)    |
| GX                            | 5 [0.5]              | 1 [0.3]                       | 6 [0.4]            |                 |
| G1                            | 69 [6.8]             | 23 [6.8]                      | 92 [6.8]           |                 |
| G2                            | 636 [62.2]           | 202 [60.1]                    | 838 [61.7]         |                 |
| G3                            | 312 [30.5]           | 110 [32.7]                    | 422 [31.1]         |                 |
| Missing                       | 17                   | 5                              | 22                 |                 |
| Chemotherapy taken during the TOSCA trial, n [%] | | | | 0.9652 |
| Folfox-4 (6 months)           | 289 [27.8]           | 93 [27.3]                     | 382 [27.7]         |                 |
| Xelox (24 weeks)              | 233 [22.4]           | 79 [23.2]                     | 312 [22.6]         |                 |
| Folfox-4 (3 months)           | 284 [27.3]           | 96 [28.2]                     | 380 [27.5]         |                 |
| Xelox (12 weeks)              | 233 [22.4]           | 73 [21.4]                     | 306 [22.2]         |                 |

\(^a\)Fisher test \( p \) value.
risk did not experienced a VTE. Overall, the accuracy of the score was 74.1%.

Survival and KS prognostic value
During the whole follow-up period, 115 (10.9%) and 34 (10.4%) patients died in the low- and intermediate-risk groups, respectively. Reasons for death are summarized in Table 5. The intermediate risk according to KS was not demonstrated to be associated to a shorter OS both at univariate [unadjusted HR (intermediate versus low risk): 0.97, 95% CI 0.66–1.42; \( p = 0.8672 \)] and multivariable analysis (HR: 0.92, 95% CI 0.63–1.36; \( p = 0.6835 \); Table 6).

At multivariable analysis, older age [HR (1 year increase): 1.04, 95% CI 1.02–1.06; \( p = 0.0002 \)] and ECOG PS equal to 1 [HR (versus 0): 2.01, 95% CI 1.13–3.60; \( p = 0.0181 \)] shortened OS, whereas a beneficial impact of the left tumor side [HR (versus right side): 0.49, 95% CI 0.35–0.68; \( p < 0.0001 \)] was detected. Finally, stage III (versus stage II) worsened OS at univariate analysis (unadjusted HR: 1.47, 95% CI 1.02–2.12; \( p = 0.0364 \)). This association was not confirmed at multivariate analysis.

Discussion
Although the TOSCA trial was not able to confirm non-inferiority of shorter adjuvant chemotherapy duration, it established that relevant hematological and nonhematological toxicities were significantly less in the 3-month arm.\(^6\) In this retrospective, post hoc analysis of this phase

| Table 3. Venous thromboembolic events. | Low risk \( n = 1053 \) | Intermediate risk \( n = 327 \) | Overall \( n = 1380 \) |
|---|---|---|---|
| Thromboembolic event, \( n \)% | | | |
| No: | 1002 (95.2) | 306 (93.6) | 1308 (94.8) |
| 3 months/12 weeks treatment duration | 500 (49.9) | 148 (48.4) | 648 (49.5) |
| 6 months/24 weeks treatment duration | 502 (50.1) | 158 (51.6) | 660 (49.5) |
| Yes: | 51 (4.8) | 21 (6.4) | 72 (5.2) |
| 3 months/12 weeks treatment duration | 28 (54.9) | 10 (47.6) | 38 (52.8) |
| 6 months/24 weeks treatment duration | 23 (45.1) | 11 (52.4) | 34 (47.2) |
| Number of thromboembolic events, \( n \)% | | | |
| One: | 48 (94.1) | 20 (95.2) | 68 (94.4) |
| Asymptomatic | 15 (32.6) | 6 (31.6) | 21 (32.3) |
| Symptomatic | 31 (67.4) | 13 (68.4) | 44 (67.7) |
| Missing | 2 | 1 | 3 |
| Two: | 3 (5.9) | 1 (4.8) | 4 (5.6) |
| Both asymptomatic | 1 (33.3) | 1 (100) | 2 (50.0) |
| Both symptomatic | 1 (33.3) | 0 (0.0) | 1 (25.0) |
| First: asymptomatic, second: symptomatic | 1 (33.3) | 0 (0.0) | 1 (25.0) |
| Thromboembolic event occurred in the first 3 months of treatment, \( n \)% | | | |
| Missing | 1 | 0 | 1 |

In the intermediate group, 298 (87.5%) and 43 (12.5%) patients had a Khorana score equal to 1 and 2, respectively.
III trial of adjuvant treatment in high-risk stage II and stage III CRC, we aimed to evaluate the thromboembolic risk and the OS predicted by the KS. The overall risk of VTEs was 5% across 1380 patients with available data. Overall, only 0.2% of patients were at high risk according to the KS, so they were excluded from all the analyses. In this population, 4.8% and 6.4% of patients in the low- and intermediate-risk groups, respectively, developed a VTE. The events occurred in the first 3 months of treatment in 40% of cases, but were not related to duration of chemotherapy. With the limitation of low number of events recorded, no variable was found to be associated with risk of VTEs (including KS, treatment duration, age, ECOG PS, sex, and stage), nor was the KS found to be associated with OS. Age, ECOG PS and tumor side were the only covariates associated

### Table 4. Risk of thromboembolic event, univariate, and multivariate logistic models.

|                        | Univariate analysis | Multivariate analysis |
|------------------------|---------------------|-----------------------|
|                        | OR 95% CI           | p value               | OR 95% CI           | p value               |
| KS: intermediate risk (versus low risk) | 1.35 (0.80–2.28)   | 0.2633                | Multivariate analysis not performed |
| Treatment duration: 3 months/24 weeks (versus 6 months/12 weeks) | 1.14 (0.71–1.83)   | 0.5931                |
| Age (1 year increase)  | 1.01 (0.98–1.03)    | 0.6045                |
| Female sex             | 0.71 (0.43–1.15)    | 0.1607                |
| ECOG performance status 1 (versus 0) | 0.94 (0.29–3.07)   | 0.9144                |
| Clinical stage III (versus II) | 0.77 (0.47–1.25)   | 0.2899                |
| Tumor site (reference right) |                        | 0.1527                |
| Left                   | 0.62 (0.38–1.01)    | 0.0527                |
| Both right and left sides | 0.82 (0.24–2.76)   | 0.7489                |

95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; KS, Khorana score; OR, odds ratio.

### Table 5. Events.

|               | Low risk n = 1053 | Intermediate risk n = 327 | Overall n = 1380 |
|---------------|-------------------|---------------------------|-----------------|
| Death, n [%]  | 115 (10.9)        | 34 (10.4)                 | 149 (10.8)      |
| Reason for death, n [%] |                        |                           |                 |
| Relapse       | 70 (60.9)         | 22 (64.7)                 | 92 (61.7)       |
| Second primary tumor | 10 (8.7)        | 3 (8.8)                   | 13 (8.7)        |
| Other disease | 9 (7.8)           | 4 (11.8)                  | 13 (8.7)        |
| Deterioration in clinical condition | 3 (2.6)           | 0 (0.0)                   | 3 (2.0)         |
| SAE           | 1 (0.9)           | 0 (0.0)                   | 1 (0.7)         |
| Other         | 1 (0.9)           | 0 (0.0)                   | 1 (0.7)         |
| Unknown       | 21 (18.3)         | 5 (14.7)                  | 26 (17.4)       |

SAE, serious adverse event.
with OS. This analysis is, however, influenced by the low number of VTEs, and is potentially not conclusive in demonstrating association of the covariates with survival.

It is well known that cancer procedures, and, in particular, colorectal resection, increase thromboembolic risk.\(^7\) For this reason, extended postoperative prophylaxis after elective surgery for cancer with low molecular weight heparin or fondaparinux (to be continued up to 5 weeks after surgery) is suggested. The risk is also associated with the start of chemotherapy in outpatients cancer subjects, with the risk being higher in upper gastrointestinal tumors and lung cancer and lower in colorectal cancer, where the rate of VTE is 0.9%, according to Khorana and colleagues.\(^8\)

Prechemotherapy platelet count and hemoglobin other than use of white cell growth factors were significant predictors of VTEs. In another population of elderly patients with stage III CRC,\(^9\) the risk was higher in older age (75–80 years) and in patients who received chemotherapy and had comorbidities evaluated according to the Charlson comorbidity index.

Overall, although the proportion of patients who experienced a VTE in our series was low, but not negligible, some lessons can be derived from these results. First, early stages of CRC represent a disease with a low–intermediate Khorana risk of VTE. Among the patients included in the current study, 76% and 24% were classified as being of low and intermediate risk according to the KS, the latter with a calculated KS equal to 1 in 87% of cases. Second, we cannot identify any predictive factor for VTEs, as the KS is not sufficiently accurate (74% of cases were well classified) to predict thromboembolic events, nor adequately prognostic for survival due to lack of correlation of intermediate risk subgroup with VTEs and OS. Third, the reduced duration of adjuvant chemotherapy (3 compared with 6 months) was not found to reduce the VTE risk. In this regard, chemotherapies used in the TOSCA trial (fluoropyrimidines and oxaliplatin) are not commonly associated with an increased risk of VTE compared with cisplatin or antiangiogenetic agents, and their role in significantly increasing the baseline risk is formally unknown but cannot be excluded.\(^10,11\) It seems conceivable that VTEs occur as a consequence of individual risk factors and underlying neoplastic disease more than duration or type of treatment. Finally, no significant effect of the Khorana risk score on prognosis was found. The reason for this is likely to be the results of the nonmetastatic stage at diagnosis, and the relatively low Khorana risk of the population evaluated, where only 0.2% of patients scored 3

---

**Table 6.** Overall survival, univariate and multivariate Cox models.

|                                      | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | HR  | 95% CI | \(p\) value | HR  | 95% CI | \(p\) value |
| KS: Intermediate risk (versus low risk) | 0.97 | [0.66–1.42] | 0.8672 | 0.92 | [0.63–1.36] | 0.6835 |
| Treatment duration: 3 months/24 weeks (versus 6 months/12 weeks) | 1.08 | [0.78–1.49] | 0.6462 |
| Age (1 year increase) | 1.05 | [1.03–1.07] | <0.0001 | 1.04 | [1.02–1.06] | 0.0002 |
| Female sex | 0.97 | [0.70–1.33] | 0.8310 |
| ECOG performance status 1 (versus 0) | 2.39 | [1.35–4.23] | 0.0027 | 2.04 | [1.14–3.64] | 0.0163 |
| Clinical stage III (versus II) | 1.47 | [1.02–2.12] | 0.0364 | 1.44 | [1.00–2.07] | 0.0512 |
| Tumor site (reference right) | <0.0001 | 0.0001 |
| Left | 0.46 | [0.33–0.64] | <0.0001 | 0.49 | [0.35–0.68] | <0.0001 |
| Both right and left sides | 0.61 | [0.25–1.50] | 0.2776 | 0.53 | [0.22–1.32] | 0.1758 |

95% CI: 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, Hazard ratio; KS, Khorana score.
points before starting chemotherapy. The KS is thus, de facto, not suitable for patients in the adjuvant setting for the aforementioned postulates. For all these reasons, we have potentially underestimated the VTE risk, and it could be higher in the unselected population treated in clinical practice. However, our data are very similar to the real-word analysis by Lyman and colleagues, where the incidence rate of VTE at 12 months from the start of chemotherapy was 6.1% in CRC.12

Other authors have attempted to evaluate the predictive and prognostic role of the Khorana risk score in clinical practice. Tafur and colleagues evaluated 7948 patients with VTEs and cancer (n = 1131 with CRC).13 In this large cohort of consecutive patients with active cancer and acute symptomatic VTE, similar to our cohort, 85% of VTEs occurred in low–intermediate Khorana risk scores in CRCs. Conversely, in a prospective cohort study of 4405 adult patients with solid tumors (n = 521 with CRC) or lymphoma initiating chemotherapy in US sites, Kuderer and colleagues found that an intermediate Khorana risk score was an independent predictor of mortality (HR: 2.31, 95% CI 1.21–4.44) compared with a low-risk score.14 Our data are also in accordance to the original validation of the score in which the positive predictive value for VTE was 7.1%.2 In SaveONCO,15 similarly, a 1608-patient primary prevention randomized study among patients with cancer, the Khorana risk score did not predict most of the VTEs, and most of the thromboembolic events (64%) occurred among patients with an intermediate risk. Recently, the Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real life patients–Cancer Associated Thrombosis study developed a new risk model based on predictors including, among others, cardiovascular risk factors, history of VTEs, and central venous catheter.19 The classification split patients into low–intermediate- and high-risk groups, where the rate of thromboembolic events was 1.7% and 13%, respectively, in the overall population, and the rate of VTEs in CRC patients (60% with localized–locally advanced disease) was 9%.

Our results have some limitations. First, this series represents a well-selected population enrolled in an adjuvant therapy phase III trial, with a nonmetastatic stage, young age (median 63 years), excellent PS (95% classified as 0), no relevant comorbidities, and adequate hematological parameters (hemoglobin and platelets), near to normal values. This is likely to be different from a real-world setting. Second, a low number of events were observed due to a low risk to experience a VTE. Moreover, only a quarter of patients were classified in the intermediate-risk group. Therefore, the statistical power could be flawed. The lack of a valid group of patients classified as high risk according to KS made the results of this analysis incomplete, and introduced the need for further analyses and discussions. Third, the risk of VTEs and mortality was not adjusted for other variables such as comorbidities or other baseline (clinical) risk factors.

In conclusion, in this subset of 1383 patients enrolled in the TOSCA trial, 1053, 327, and 3 patients were classified as at low, intermediate,
and high risk of VTE, respectively; 4.8% of patients in the low risk group and 6.4% of patients in the intermediate risk group experienced VTEs. Considering only the low and intermediate risk group, Khorana risk score was not found to independently predict the risk of thromboembolic events, and its accuracy was 74%. Currently, no studies have explored the role of thromboprophylaxis in the adjuvant CRC setting; its role in clinical practice remains unclear and should be investigated intensively.

Acknowledgements
GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell’Apparato Digerente - Ufficio Operativo): L. Frontini, S. Rota, L. Cozzi.

Funding
The author(s) received no financial support for the research, authorship, and publication of this article.

Conflict of interest statement
The authors declare that there is no conflict of interest.

ORCID iDs
Gerardo Rosati https://orcid.org/0000-0001-7004-6862
Lorenza Rimassa https://orcid.org/0000-0001-9957-3615
Fausto Petrelli https://orcid.org/0000-0001-9639-4486

References
1. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. Blood 2013; 122: 1712–1723.

2. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008; 111: 4902–4907.

3. Metcalf RL, Al-Hadithi E, Hopley N, et al. Characterisation and risk assessment of venous thromboembolism in gastrointestinal cancers. World J Gastrointest Oncol 2017; 9: 363.

4. Mandalà M, Barni S, Prins M, et al. Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial. Ann Oncol 2009; 21: 871–876.

5. Sobrero A, Lonardi S, Rosati G, et al. FOLFOX or CAPOX in stage II to III colon cancer: efficacy results of the italian three or six colon adjuvant trial. J Clin Oncol 2018; 36: 1478–1483.

6. Lonardi S, Sobrero A, Rosati G, et al. Phase III trial comparing 3–6 months of adjuvant FOLFOX4/XELOX in stage II–III colon cancer: safety and compliance in the TOSCA trial. Ann Oncol 2016; 27: 2074–2081.

7. Auer RAC, Scheer AS, McSparron JJ, et al. Postoperative venous thromboembolism predicts survival in cancer patients. Ann Surg 2012; 255: 963–970.

8. Khorana AA, Francis CW, Culakova E, et al. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer 2005; 104: 2822–2829.

9. Hanna N, Bikov K, McNally D, et al. Impact of venous thromboembolism on mortality of elderly Medicare patients with stage III colon cancer. Oncologist 2012; 17: 1191–1197.

10. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA 2008; 300: 2277–2285.

11. Seng S, Liu Z, Chiu SK, et al. Risk of venous thromboembolism in patients with cancer treated with Cisplatin: a systematic review and meta-analysis. J Clin Oncol 2012; 30: 4416–4426.

12. Lyman GH, Eckert L, Wang Y, et al. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. Oncologist 2013; 18: 1321–1329.

13. Tafur AJ, Caprini JA, Cote L, et al. Predictors of active cancer thromboembolic outcomes: RIETE experience of the Khorana score in cancer-associated thrombosis. Thromb Haemost 2017; 117: 1192–1198.

14. Kuderer NM, Culakova E, Lyman GH, et al. A validated risk score for venous thromboembolism is predictive of cancer progression and mortality. Oncologist 2016; 21: 861–867.

15. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 2012; 366: 601–609.

16. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica 2019; 104: 1277–1287.
17. Di Nisio M, Porreca E, Ferrante N, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev* 2012; 2: CD008500.

18. Riedl JM, Posch F, Bezan A, et al. Patterns of venous thromboembolism risk in patients with localized colorectal cancer undergoing adjuvant chemotherapy or active surveillance: an observational cohort study. *BMC Cancer* 2017; 17: 415.

19. Gerotziafas GT, Taher A, Abdel-Razeq H, et al. A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS–cancer-associated thrombosis study. *Oncologist* 2017; 22: 1222–1231.