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External validation of COMPASS and BIOSCOPE prognostic scores in colorectal peritoneal metastases treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)

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ABSTRACT

Introduction: The selection of patients undergoing cytoreductive- surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is crucial. BIOSCOPE and COMPASS are prognostic scores designed to stratify survival into four classes according to clinical and pathological features. The purpose of this study is to analyze the prognostic role of these scores using a large cohort of patients as an external reference.

Methods: Overall survival analysis was performed using Log-Rank and Kaplan-Meier curves for each score. The probability of survival at 12, 36, and 60 months was tested using receiver operating characteristic (ROC) curves to determine sensitivity and specificity.

Results: From the validation cohort of 437 patients, the analysis included 410 patients in the COMPASS group and 364 patients in the BIOSCOPE group (100% data completeness). We observed a different patient distribution between classes (high-risk for BIOSCOPE compared to COMPASS, $p = 0.0001$). Nevertheless, both COMPASS and BIOSCOPE effectively stratified overall survival (Log-Rank, $p = 0.0001$ in both cases), with a lack of discrimination between COMPASS classes II and III ($p =$ n.s.). COMPASS at 12 m and BIOSCOPE at 60 m showed the best performance in terms of survival prediction (AUC of 0.82 and 0.81). The specificity of the two tests is good (median 81.3%), whereas sensibility is quite low (median 64.2%).

Conclusion: Following external validation in a large population of patients with CRC-PM who are eligible for surgery, the COMPASS and BIOSCOPE scores exhibit high inter-test variability but effectively stratify cancer-related mortality risk. While the quality of the scores is similar, BIOSCOPE shows better inter-tier

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differentiation, suggesting that tumor molecular classification could improve test discrimination capability. More powerful stratification scores with the inclusion of novel predictors are needed.

1. Introduction

Colorectal cancer (CRC) is the third most common neoplasm in developed countries and peritoneal metastases (PM) are the cause of death in a large number of patients [1–3]. The survival of isolated CRC-PM patients is shorter (16.3 months) compared to all other isolated metastatic sites [4]. Multimodal treatment, which included cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC), prolonged the survival of selected CRC-PM patients by up to 45 months [5–7]. The selection of patients who stand to benefit the most from surgery and the exclusion of unnecessary procedures is of paramount importance.

The evolution of the study of prognostic factors in CRC-PM patients selected for surgery, which began in the late 1990s with the analysis of surgical, pathological, and clinical features, progressed to the tumor's mutational profiling in recent years. It has been found that residual tumor after surgery (measured with completeness of cytoreduction, CC score ranging from 0 to 3) and the extent of peritoneal disease (calculated with the peritoneal cancer index, PCI ranging from 0 to 39) have been demonstrated to be the most reliable predictors of survival [8]. The pathological characteristics of primary tumors such as nodal status (N) and differentiation grade (G), or the presence of signet-ring cells (SRC) have also been reported as prognostic factors [8,9]. More recently, genetic mutations of the RAS and RAF genes, as well as microsatellite status (MS), have gained relevance for guiding chemotherapeutic treatment and possibly predicting prognosis [10]. In recent years, different prognostic scores, including some of the previous factors, have been proposed to stratify survival after the CRS-HIPEC procedure. Such scores have been thought to improve patients' selection process, but there are still some limitations in clinical use, since some factors are preoperatively unknown (such as PCI, N status in synchronous PM or completeness of cytoreduction). The most relevant scores are the prior surgical score PSDSS (Peritoneal Surface Disease Severity Score), COMPASS (colorectal peritoneal metastases prognostic surgical score), and BIOSCOPE (BIOlogical Score of COlorectal PEritoneal metastasis) [11–13]. Due to missing central revision of symptoms severity (one of the PSDSS score items), PSDSS was excluded in the analysis.

The aim of this study is to validate the prognostic role of two of these scores (COMPASS and BIOSCOPE) using an external large validation cohort of patients treated with CRS-HIPEC.

2. Methods

2.1. Data collection and patients

Clinical, pathological, operative, and postoperative data from 13 Italian centers with expertise in peritoneal malignancies were collected retrospectively in a centrally maintained database. All participating institutions are referral centers forming part of a scientific collaborative group (Peritoneal Surface Malignancies Oncoteam) affiliated with the Italian Society of Surgical Oncology (SICO) and certified by the SICO for the surgical treatment of PM. The study was approved by the Ethics Committee of the lead center (the Veneto Institute of Oncology-IOV, Padua, no. 194/2019). All patients were treated according to national guidelines for CRC-PM, following the multidisciplinary tumor board's discussion and selection for CRS-HIPEC. Cytoreductive surgery and HIPEC were performed according to standard operating procedures [14].

2.2. Statistical analysis

Continuous variables were reported using the median and a 95% confidence interval (95% CI), while frequency counts and percentages were used for categorical variables. Cancer-specific survival was defined as the time interval between CRS-HIPEC and the date of death from CRC recurrence. Patients without a documented event were censored at the last known date. All patients with missing data on determining COMPASS or BIOSCOPE variable calculations were excluded from analysis. The COMPASS and BIOSCOPE scores were calculated using data from the validation cohort in accordance with the respective authors' scoring systems. The distribution of cases under observation between the two scores was analyzed using the Chi-Square test. Survival curves were estimated with the non-parametric Kaplan-Meier method, and the log-rank test was used to compare strata. Prediction of survival probability at 12, 36, and 60 months was tested using receiver operating characteristic (ROC) curves, and the optimal cut-off for sensitivity and specificity for each score and time point was determined using the Youden index. All statistical tests were two-sided, and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS v. 20.0 (SPSS Inc., Chicago, IL) and GraphPad Prism v. 9 (GraphPad Software, San Diego, CA, US).

3. Results

The COMPASS score validation cohort consisted of 410 patients with complete data (age, PCI, N status, and SRC), while the BIOSCOPE cohort included 364 (PCI, N status, G, and KRAS/BRAF mutation). Table 1 summarizes the patient characteristics and frequency distributions for these parameters and Supplementary Material Table 4 reports all patients' characteristics. We observed a lower prevalence of signet-ring cells and a younger age at operation in the validation group compared to the COMPASS data, but higher PCI values and differentiation grade in the validation group compared to BIOSCOPE data (all p-values < 0.0001). All the remaining variables were similar (p = n.s.). In our series, 70% of cases received pre-CRS/HIPEC and 52% post systemic chemotherapy; 79% of patients received chemotherapy prior to CRS/HIPEC and 61% after in the BIOSCOPE cohort, whereas only 17.5% of patients received neoadjuvant and 65% adjuvant chemotherapy in COMPASS group.

The distribution of validation cohort patients differs for the two scores (Chi-Square test $p = 0.0001$). In reality, COMPASS demonstrates an almost equivalent distribution across the four tiers (with a tendency for low-risk classes I-II accounting for 57.1% of patients), whereas BIOSCOPE stratifies patients into high-risk classes (76.3% of patients in classes C-D and none in the lowest risk class A) (Table 2).

Nevertheless, the two COMPASS and BIOSCOPE scores effectively stratified overall survival, as demonstrated by Kaplan-Meier curves with a Log-Rank p-value of 0.0001 in both cases, with good discrimination between each score tier (all but one pairwise

Table 1
Score variables based on patient characteristics.

		Validation group		Reported		p
		n	%	n	%	
COMPASS	**Age**	57.3*	10.9**	61.3*	10.6**	0.0001
	PCI	9.7*	6.4**	8.7*	5.2**	0.06
	SRC	9	2.2	13	6.5	0.031
	N0–N1	247	60.2	119	59.7	0.916
	N2	163	39.8	80	40.3	
BIOSCOPE	**PCI 0–10**	206	56.6	375	71.6	0.0001
	PCI 10–20	136	37.4	111	21.1	
	PCI > 20	22	6.0	9	7.1	
	N0	117	32.1	80	25.6	0.127
	N1	109	30.0	111	35.5	
	N2	138	37.9	122	39.0	
	G1	23	6,3	86	23.6	0.0001
	G2	183	50.3	200	55.0	
	G3	158	43.4	78	21.4	
	Wild-type	173	42.6	192	50.8	0.196
	KRAS mut	166	45.6	145	38.4	
	BRAF mut	29	8.0	22	5.8	

Note. *: mean, **: standard deviation, n: number of cases, %: percentage of n, SRC: signet-ring cell, mut: mutated. Reported: data obtained from original articles [12,13]. P-values obtained with the Chi-Square test or the T-Test.

Table 2
Distribution and survival analysis by score classification.

		Patient distribution (p 0.0001*)		ESTIMATED SURVIVAL ANALYSIS						
				Reported			Validation group			p
		n	%	MS	95%CI		MS	95%CI		Log Rank
COMPASS (n 410)	**I**	155	37.8	n.e	n.e.	n.e.	95.0	n.e.	n.e.	0.00001
	II	79	19.3	37.7	28.5	n.e.	45.1	34.6	55.6	
	III	91	22.2	25.0	21.3	47.5	38.9	29.7	48.2	
	IV	85	20.7	16.5	13.0	24.0	20.7	17.8	23.6	
BIOSCOPE (n 364)	**A**	0	0	70.0	58.0	82.0	–	–	–	0.00001
	B	86	23.6	55.0	42.0	68.0	n.e.	n.e.	n.e.	
	C	236	64.9	33.0	24.0	41.0	38.8	32.1	45.5	
	D	42	11.5	13.0	5.0	24.0	22.1	14.6	29.6	

Note. n: number of cases; MS: median survival in months; n.e.: not estimable; 95% CI: 95% confidence interval; -: no cases. * Chi-square p-value of COMPASS and BIOSCOPE class distribution; reported: data obtained from original articles [12,13].

Log-Rank p-value < 0.0001), with the exception of COMPASS classes II and III (estimated median survival of 45.1 and 38.9, pairwise Log-Rank p = 0.345) (Fig. 1).

When ROC curves were used to analyze survival prediction at different time points (12, 36, and 60 months), COMPASS performed best at 12 months (AUC of 0.82, 95% CI 0.73–0.91), with 87% specificity and 74% sensitivity. At 36 and 60 months, the prediction capability of COMPASS remains reasonable (AUC of 0.74 and 0.77, respectively). BIOSCOPE has the best prediction capability at 60 months (AUC of 0.81, 95% CI 0.74–0.88), with 75% specificity and

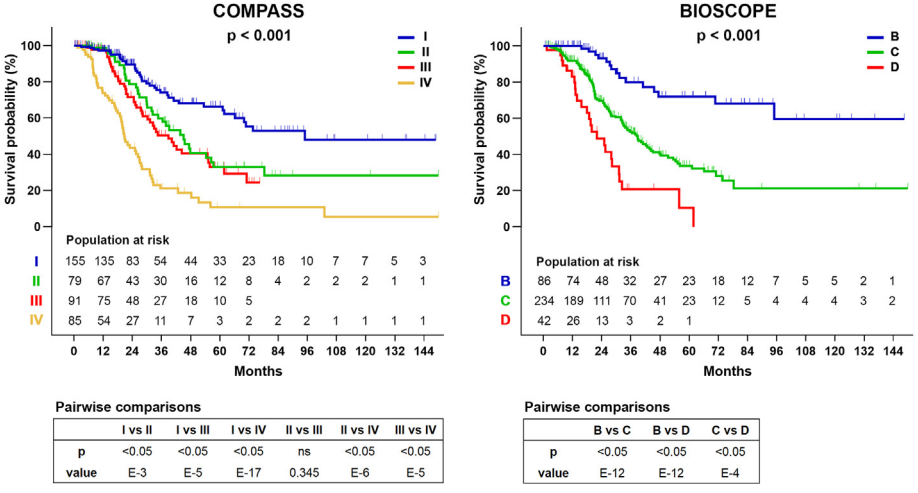

Fig. 1. Validation cohorts' survival curves.
Note. E: Base-10 exponential of p-value; p-values obtained with Log-Rank test.

70% sensitivity. However, BIOSCOPE quality at 12 and 36 months remains acceptable (AUC of 0.76 and 0.71, respectively). (Table 3, Fig. 2).

With regard to the Youden index calculation, the optimal cut-off value for the discrimination of survival probability for each score at each time point reveals that COMPASS has a higher variation in optimal cut-off values (range width of 33 points, 20.6% of the score value) than BIOSCOPE (range width 2 points, 16.7% of the score value). In both scores, Youden indexes (and, therefore, optimal cut-off values) decrease with increasing survival expectancy up to 60 months (from 85 to 52 points for COMPASS, and from 6.5 to 4.5 for BIOSCOPE). In general, both tests tend to have better specificity (median of 81.3%) than sensitivity (64.2%) (Table 3).

4. Discussion

Given the morbidity and cost associated with cytoreductive surgery for CRC-PM, there has always been a strong interest in identifying prognostic factors for surgery eligibility. Complete cytoreduction and the Peritoneal Cancer Index are the most important and extensively used selection criteria in clinical practice, although these factors are not accurately defined and quantified prior to surgical exploration. Other clinical and pathological factors, such as nodal status (N), differentiation grade (G), or the presence of signet-ring cells (SRC) [8,9] have been shown to be independently associated with prognosis following CRS-HIPEC and, accordingly, some prognostic scores have been proposed over the years by assembling combined risk factors.

Verwaal et al. proposed the predictive score (PS) in 2004. It is based on primary tumor location (colon vs. rectum), differentiation, and peritoneal extension (on a 7-tier classification) [5]. In 2012, Cashin et al. proposed the COREP (colorectal peritoneal) score based on a single histological feature (signet-ring cell, SRC) plus preoperative serum marker values and kinetics [15,16].

In 2010, Chua et al. proposed one of the most widely used predictive scores, termed PSDSS (peritoneal surface disease severity score), which was further validated a few years later by Esquivel et al. in a large series of one thousand CRC patients [11,17]. PSDSS is a 4-tiered score that takes patients' symptoms, PCI, and tumor grading into account. Once published, different authors reported PSDSS' low predictive capability and lack of objectivity for some score categories, such as “mild abdominal pain” or “symptomatic/asymptomatic ascites” [16,17]. Following an external validation of PSDSS, Simkens et al. proposed a novel scoring system called COMPASS (colorectal metastases prognostic surgical score) in 2016. COMPASS is a 4-tier (class I-IV) scoring system ranging from 0 to 200 points and takes into account clinical and pathological characteristics such as age, PCI, primary tumor nodal status (N), and SRC (Fig. 3) [12].

After it was demonstrated that KRAS mutations impede response to anti-epidermal growth factor receptor (EGFR) targeted therapy, systematic detection of mutational status was introduced into clinical practice [18,19]. The negative prognostic role of RAS and RAF mutations was first reported in liver and lung metastatic CRC patients [20,21], and more recently with peritoneal metastases [10]. Arjona et al. were the first to identify the role of RAS mutational status as an independent prognostic factor in patients treated with CRS-HIPEC for CRC-PM, by combining the KRAS mutational status with the PSDSS score [22].

The first comprehensive scoring system combining mutational status and clinical/pathological characteristics was proposed by Schneider et al., in 2019. The score, termed BIOSCOPE (BIOlogical Score of COlorectal PEritoneal metastasis), was developed in a large cohort (358 patients) and validated in a control group (136 patients). BIOSCOPE has four classes (A-D) and is calculated using PCI, N status, Grading (G), KRAS, and BRAF mutations (Fig. 3) [13]. More recently, an Italian collaborative group performed a prognostic analysis on a large cohort of patients and found nearly identical molecular predictive factors to those identified in the BIOSCOPE study [14].

We used COMPASS and BIOSCOPE scores for validation because those are the most recent and objective prognostic tools in CRC-PM. Our results confirm that both scores are able to efficiently stratify cancer-related mortality risk and give an acceptable survival prediction in CRC-PM patients selected for surgery.

Calculation of scores in the validation cohort shows different distributions of patients across the four classes of the two scores ($p = 0.0001$): a homogeneous distribution with a tendency toward low-risk classes for COMPASS, and a predominance of high-risk tiers for BIOSCOPE. Additionally, none of our 364 patients are classified as BIOSCOPE class A, compared to 25% of patients in the original article. BIOSCOPE class A requires a total of zero points and is the only class without a range of values (2–4 points for classes B to D); to be considered in BIOSCOPE class A, one patient has to be simultaneously PCI <10, N0, G1/G2, and wild-type (Fig. 3). This could reflect different characteristics between the two populations, such as a high prevalence of G3 and high PCI in our cohort ($p < 0.0001$, see Table 1) and a slightly higher mutational rate of KRAS, 46% vs. 38% (p = n.s.).

Besides distribution differences, both scores successfully stratify survival in our validation cohort (Log-Rank $p = 0.0001$). The only exceptions are COMPASS classes II and III, since the difference in estimated median survival between these two classes is only 7 months in the validation cohort (pairwise Log-Rank p = n.s.). As for BIOSCOPE class A, a possible explanation is the relative difference in class width according to the scoring system because COMPASS tiers II-III have a reduced range of values, meaning the inclusion of similar patients in our series (together, class II and III have a width of 30 points out of 200, whereas class I has a range of 52 points and class IV of 120).

The analysis of survival prediction using the two scoring systems demonstrates that the test is of fair to good quality, as

Table 3
Survival prediction using ROC curve scores at different time-points.

Survival probability analysis		ROC					
		AUC	%95 CI		Score cut-off	Sensitivity	Specificity
12 m	**COMPASS**	0.818	0.726	0.909	85.9	74.1	86.7
	BIOSCOPE	0.762	0.674	0.850	6.5	58.3	82.4
36 m	**COMPASS**	0.737	0.677	0.769	68.7	58.1	80.3
	BIOSCOPE	0.706	0.639	0.773	6.5	36.2	90.5
60 m	**COMPASS**	0.774	0.706	0.843	52.1	81.1	60.3
	BIOSCOPE	0.805	0.735	0.876	4.5	70.0	74.5

Note. ROC: receiver operating characteristic; AUC: area under the curve; 95% CI: 95% confidence interval; Score cut-off: score value with best discrimination for survival at each time-point (corresponding to the Youden index).

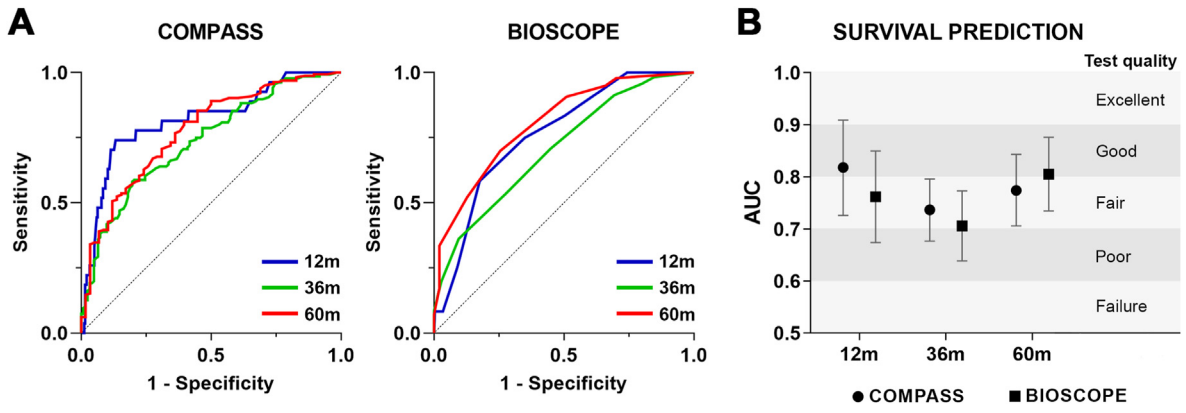

Fig. 2. ROC curves and score quality.
Note. **A:** ROC curves of COMPASS and BIOSCOPE scores at 12, 36, and 60 months. Dotted lines: AUC = 0.5. **B:** Visual test quality for survival prediction at different times. Whiskers: 95% confidence interval of AUC.

COMPASS

Variable	Risk points
Age	
(per 10 years)	**5.74 points/10 years** 20 years = 0 points
Peritoneal Cancer Index	
(per PCI point)	**3.33 points/PCI point** PCI 0 = 0 points
Lymph node status	
N0/N1	**0**
N2	**19.22**
Signet ring cell histology	
No	**0**
Yes	**39.30**

I	II	III	IV
0 – 51.9	51.9 – 64.7	64.7 – 82.0	≥ 82.0

BIOSCOPE

Variable	Risk points
Peritoneal Cancer Index	
PCI 1–10	**0**
PCI 11–20	**2**
PCI > 20	**4**
Lymph node status	
N0	**0**
N1	**2**
N2	**3**
Differentiation grade	
G1/G2	**0**
G3	**2**
RAS/RAF mutation status	
Wild-type	**0**
K-Ras mutation	**1**
B-Raf mutation	**3**

A	B	C	D
0	1 – 3	4 – 7	8 – 12

Fig. 3. Summary of COMPASS and BIOSCOPE scores.

determined by the AUC derived from the ROC curves for survival probability at different time points. COMPASS obtained the best results at 12 months and BIOSCOPE at 60 months (AUC of 0.8). All other calculated AUCs are above 0.7, which qualifies the test as fair in terms of ROC quality. Internal confirmation of test reliability is provided by the fact that the optimal discrimination cut-offs for both scores (Youden indexes) decrease with longer life expectancy periods, since tests have to be more restrictive to predict long-term survival. The limited AUC variations for the same tests over time can be explained by the different size of the population exposed to risk during the follow-up period, which physiologically decreases after 5 years, rather than the patients' pathological or molecular features. Specificity is good for both scores, whereas sensitivity is just adequate, consistent with generally fair AUC values.

This study's main limitation is that the BIOSCOPE score was evaluated as a 3-tier test only, since no patient in the validation cohort met the criteria for inclusion in the lowest-risk class. This discrepancy is quite surprising, especially in terms of percentage deviation (25.6% in class A of the BIOSCOPE cohort versus 0% in the validation cohort), and underlines the wide variation in the selection process and possibly in the pathological reporting (particularly regarding tumor grade) that exists among peritoneal cancer centers.

Another drawback of these scores, is that some prediction factors are determined only after surgery (such as actuarial PCI, N-status and signet ring cells in case of synchronous metastases), *de-facto* limiting their clinical usefulness as selection criteria.

At the present, parameters used in both scores should be considered during multidisciplinary board to guide decision process, as proposed in a recent consensus, whereas many centers accept as selection criteria the (estimated) PCI below 15/20 points and the completeness of cytoreduction [23].

There is still a debate about the role of systemic chemotherapy in patients affected by peritoneal metastases eligible for cytoreductive surgery. According to different reports, the lack of robust evidence about the efficacy or timing of chemotherapy administration, determines different approaches among centers [24,25]. Use of preoperative chemotherapy could act as a selection criteria and this may explain different survivals of BIOSCOPE cohort (42 months) and our series (43 months) in which the majority of patients have been pre-treated compared to patients in COMPASS cohort (35 months), that received neoadjuvant chemotherapy only in 17.5% of cases [25–28]. A sub-analysis performed in our series according to administration of chemotherapy, confirms quite good prediction capability of both scores (data not shown), with limitations related to reduced sample size of chemo-naive patients. Role of chemotherapy in CRC-PM could be addressed by an on-going trial (CAIRO6), even though its role as "selection criteria" should be further investigated [29].

In the near future, the implementation and integration of the

two scores with other factors will probably lead to a more robust predictive system; for example, the role of chemotherapy and presence of signet-ring cells (SRC) are not considered in the scores. Despite the fact that SRC had a significant predictive role in our and COMPASS patients (HR 2.4 and 3.7, respectively), it is not included in BIOSCOPE. Nevertheless, both scores are found to have a good survival discrimination capability and a similar quality (both their best AUC is just above 0.8), even though BIOSCOPE exhibits superior inter-tier differentiation due to the absence of overlapping classes. This consideration suggests that, tumor mutational analysis could improve test discrimination capabilities [9]. Further improvements could be obtained by investigating the role of chemotherapy, RAS and RAF mutations, possibly related to different biological behaviors [30], as well as the analysis of the microsatellite instability that could mitigate RAS and RAF mutations' detrimental effects on survival, as recently reported [14].

5. Conclusions

After external validation in a large population of patients with CRC-PM who are eligible for CRS, it was determined that COMPASS and BIOSCOPE scores have high inter-test variability but effectively stratify cancer-related mortality risk and provide acceptable survival prediction. While the score quality is similar, BIOSCOPE demonstrates superior inter-tier differentiation applied to our series, suggesting that tumor molecular classification may improve test discrimination capability. Taking these factors into account, efforts have to be made to identify more powerful stratification scores that incorporate novel predictors.

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CRediT authorship contribution statement

Marco Tonello: Conceptualization, Writing – original draft, Data curation, and collection. **Dario Baratti:** Validation. **Paolo Sammartino:** Validation. **Andrea Di Giorgio:** Data curation, and collection. **Manuela Robella:** Data curation, and collection. **Cinzia Sassaroli:** Data curation, and collection. **Massimo Framarini:** Data curation, and collection. **Mario Valle:** Data curation, and collection. **Antonio Macrì:** Data curation, and collection. **Luigina Graziosi:** Data curation, and collection. **Paola Fugazzola:** Data curation, and collection. **Piero Vincenzo Lippolis:** Data curation, and collection. **Roberta Gelmini:** Data curation, and collection. **Daniele Biacchi:** Data curation, and collection. **Shigeki Kasamura:** Data curation, and collection. **Marcello Deraco:** Data curation, and collection. **Carola Cenzi:** Data curation, and collection. **Paola Del Bianco:** Statistical analysis, Data curation, and collection. **Marco Vaira:** Data curation, and collection. **Antonio Sommariva:** Conceptualization, Writing – original draft, Data curation, and collection.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.10.007.

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