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Prognostic value of total tumor volume in patients with colorectal liver metastases: A secondary analysis of the randomized CAIRO5 trial with external cohort validation

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ABSTRACT

Background: This study aimed to assess the prognostic value of total tumor volume (TTV) for early recurrence (within 6 months) and overall survival (OS) in patients with colorectal liver metastases (CRLM), treated with induction systemic therapy followed by complete local treatment.

Methods: Patients with initially unresectable CRLM from the multicenter randomized phase 3 CAIRO5 trial (NCT02162563) who received induction systemic therapy followed by local treatment were included. Baseline TTV and change in TTV as response to systemic therapy were calculated using the CT scan before and the first after systemic treatment, and were assessed for their added prognostic value. The findings were validated in an external cohort of patients treated at a tertiary center.

Results: In total, 215 CAIRO5 patients were included. Baseline TTV and absolute change in TTV were significantly associated with early recurrence ($P = 0.005$ and $P = 0.040$, respectively) and OS in multivariable analyses ($P = 0.024$ and $P = 0.006$, respectively), whereas RECIST1.1 was not prognostic for early recurrence ($P = 0.88$) and OS ($P = 0.35$). In the validation cohort ($n = 85$), baseline TTV and absolute change in TTV remained prognostic for early recurrence ($P = 0.041$ and $P = 0.021$, respectively) and OS in multivariable analyses ($P < 0.0001$ and $P = 0.012$, respectively), and showed added prognostic value over conventional clinicopathological variables (increase *C*-statistic, 0.06; 95 % CI, 0.02 to 0.14; $P = 0.008$).

Conclusion: Total tumor volume is strongly prognostic for early recurrence and OS in patients who underwent complete local treatment of initially unresectable CRLM, both in the CAIRO5 trial and the validation cohort. In contrast, RECIST1.1 did not show prognostic value for neither early recurrence nor OS.

1. Introduction

For patients with colorectal liver metastases (CRLM), local treatment is the only potentially curative treatment option [1–3]. Local treatment includes complete surgical resection of all metastases, local ablative techniques like radiofrequency ablation or microwave ablation, or a combination of these modalities. Unfortunately, 80 % of patients present at diagnosis with unresectable CRLM due to too extensive disease or metastases at crucial locations [3,4]. Technical resectability of CRLM is defined as the ability to resect all measurable metastases, on the condition that the future remnant liver covers 25–30 % of the total liver volume in case of no underlying liver disease, with the preservation of adequate vascular flow and biliary drainage [5,6]. Patients with initially technically unresectable CRLM can become eligible for local treatment if their tumor load is reduced upon induction with systemic therapy [7,8].

Treatment decision making for patients with CRLM is predominantly based on arguments involving this technical resectability, while the question remains if local treatment is clinically beneficial for each individual patient. There is growing interest in how a shift can be made from technically driven surgery to biologically driven surgery. Biologically driven surgery aims to select individual patients for the optimal treatment strategy, including local treatment to achieve long-term survival and cure, taking into consideration the underlying tumor biology. This includes genetic mutations, response to induction systemic therapy, and other clinical and biological parameters [9,10].

In patients with unfavorable tumor biology undergoing local treatment for CRLM, the clinical benefit of local treatment may be limited. Approximately 60 % of patients undergoing local treatment for CRLM develops recurrence within two years after treatment, with an overall recurrence rate of 80 % [11–14]. Patients with early recurrence (within 6 months) have a significantly worse prognosis than patients with late recurrence (after 6 months). The 5-year overall survival is 25.9 % for patients with early recurrence and 53.1 % for patients with late recurrence [12]. It is hypothesized that timing of hepatic recurrence reflects underlying tumor biology and that early recurrence is associated with prognostic unfavorable tumor biology [15]. Early recurrence cannot adequately be predicted with currently available clinical and biological factors in patients with initially unresectable CLRM. Therefore, resectability assessment currently remains primarily a technical and anatomical decision [16].

Over the past decades, clinical and biological characteristics potentially reflecting unfavorable tumor biology were proposed to determine risk profiles for early recurrence and limited overall survival (OS) after local treatment in the individual patient, such as the Fong and GAME score [17–19]. However, those risk scores have suboptimal predictive performance for adequate guidance in clinical decision-making for patients with secondarily technically resectable CRLM [20,21].

In a previous study, change in total tumor volume (TTV) was suggested to be prognostic for recurrence-free survival (RFS) in patients with initially unresectable CRLM, who became eligible for resection after induction with systemic therapy. Tumor response according to Response Evaluation Criteria in Solid Tumors (RECIST1.1) was not prognostic [22]. Preoperative TTV was also shown to be prognostic for OS and RFS in patients with primary resectable CRLM [23]. These studies, however, did not validate their findings externally and did not assess the prognostic value of both baseline TTV and TTV change during systemic therapy. Baseline TTV and TTV change during systemic therapy together could act as prognostic factors, potentially contributing to biologically driven surgery [23].

This study aimed to assess the prognostic value of baseline TTV and TTV change during systemic therapy for early recurrence and OS in patients with CRLM treated with induction systemic therapy followed by complete local treatment, and to validate these findings in an external patient cohort.

2. Methods

2.1. Study population

Patients registered between 2014 and 2022 from the multicenter randomized phase 3 trial of the Dutch Colorectal Cancer Group, CAIRO5 (NCT02162563) were included for primary analyses (Supplement S1) [24,25]. In this trial, patients with initially unresectable liver-only CRLM were randomized between different systemic therapy combinations based on primary tumor site and genetic mutation status (*RAS/-BRAF*^{V600E}). Treatment regimens consisted of doublet or triplet chemotherapy (FOLFOX/FOLFIRI or FOLFOXIRI) in combination with targeted therapy (either bevacizumab or panitumumab). In the current study, only CAIRO5 patients were included in whom complete local treatment was achieved after induction systemic therapy. Local treatment was considered complete if no evidence of residual tumor was present in the liver after local treatment.

As a validation cohort, patients diagnosed with liver-only CRLM who underwent complete local treatment after systemic treatment were retrospectively identified from electronic health records in Erasmus MC Rotterdam (EMC). These patients were either initially unresectable or upfront resectable and based on this resectability status received systemic treatment accordingly [26]. Medical files of patients with CRLM

from 1 January 2010 to the 1st of January 2021 were reviewed.

The following patient data were collected: patient and tumor characteristics, including demographics, primary colorectal tumor sidedness, genetic mutation status (*RAS/BRAF*^{V600E}), serum CEA, systemic treatment regimen and pre- and only the first post systemic treatment contrast-enhanced CT scans in portal venous phase. RECIST1.1 was only available in the CAIRO5 trial, as it Is not routinely assessed in daily clinical practice. The definitions used are shown in Supplement S2.

2.2. Total tumor volume quantification

In pre-treatment and only the first post-treatment CT scans all CRLM were segmented with semi-automatic software in the Tumor Tracking Modality of IntelliSpace Portal 9.0® (Philips, Best, The Netherlands) by one trained member of the research team (MZ, NW, AJB). All segmentations were verified and, if needed, adjusted by one abdominal radiologist (JHvW, JvdB, SM, IN). The TTV was calculated in the SAS analytical platform® using the *quantifyBioMedImages* action [27]. This action calculates TTV directly out of the tumor segmentation from all CRLM, based on the voxel size and the number of voxels included in the segmentation [22]. TTV was assessed at baseline prior to systemic induction therapy and at the first post-treatment scan. To determine TTV response to systemic therapy, the absolute difference in pre-treatment TTV and first post-treatment TTV was calculated in milliliters.

2.3. Early recurrence and overall survival

Early recurrence was defined as any recurrence within six months from the date of last local liver treatment. Patients were censored at the last clinical visit date if there was no recurrence or if they had died without recurrence. Overall survival was calculated in months from the date of randomization (CAIRO5) or the date of detection of liver metastases (EMC) to the date of death or date of last clinical visit.

2.4. Statistical analysis

Continuous and categorical baseline characteristics are presented as median (interquartile range [IQR]) or as frequencies and percentages and were compared using the Mann-Whitney *U* test or Pearson chi-squared test, respectively. Median follow-up was estimated using the reverse Kaplan-Meier method.

The membership model *C*-statistic was estimated to summarize the extent to which the discovery and validation cohort differed from each other [28]. High membership model *C*-statistic values (i.e., close to 1) reflect substantial differences in baseline characteristics between the discovery and validation cohort and indicate that the external validation process assesses generalizability. In contrast, low membership model *C*-statistic values (i.e., close to 0.5) indicate that the discovery and validation cohort are similar in baseline characteristics, implying that the external validation process merely assesses statistical reproducibility.

Multivariable Cox regression modeling was used to assess the added prognostic value of baseline TTV and change in TTV and other size-based variables (i.e. RECIST1.1 and tumor burden score (TBS [29]) after adjusting for a comprehensive set of variables: (a) all balancing variables used in the stratification procedure for the CAIRO5 trial (i.e., resectability of liver metastases, serum LDH level, choice of irinotecan vs oxaliplatin, and *RAS/BRAF* mutation status), and (b) additional prognostic variables (i.e., age, sex, serum CEA level, number of metastases, diameter of largest metastasis, site of primary tumor, distribution of liver metastases, and time to metastasis). Relative change in TTV was not explored, as this variable showed high collinearity with absolute change in TTV, and showed no additional prognostic value over absolute change in TTV in preliminary analyses. See Supplement S3 for additional information regarding the statistical analysis.

A two-sided P value lower than 0.05 was considered statistically significant. All statistical analyses were performed using R, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata, version 17 (StataCorp).

3. Results

3.1. Study population

In total, 310 of 521 eligible patients from the CAIRO5 trial were suitable for local treatment, of whom 215 were included in this study. For the external validation cohort, 85 of 178 eligible patients were included (Fig. 1). The external validation dataset differed considerably from the CAIRO5 trial in terms of baseline characteristics (membership model *C*-statistic, 0.87; 95 % CI, 0.83–0.91). Specifically, patients in the CAIRO5 trial had a higher median number of metastases (9 [IQR, 6–15] vs 4 [2–6]; $P < 0.0001$) and higher median serum level of CEA (34 [9–139] vs 16 [5–42]; $P = 0.002$; Table 1). However, there were no substantial differences between the CAIRO5 cohort and external validation cohort in terms of age (median [IQR], 62 [54–70] vs 62 [54–67], $P = 0.58$) and sex (37 % female vs 33 %, $P = 0.54$). The median time between the CT scan at baseline and the first follow-up CT-scan was 2.3 months (IQR, 2.1–2.5 months) for the CAIRO5 cohort and 3.0 months (2.5–3.8 months) for the validation cohort.

3.2. Total tumor volume

in the CAIRO5 cohort of patients with CRLM, median TTV at baseline was 48 mL (IQR, 17–178; Table 1), the median absolute change in TTV was –22 mL (–81 to –6) and the median relative change in TTV –60 % (–73 to –44). In the external validation cohort, baseline TTV was lower with a median TTV of 28 mL (9–62). Median absolute change in TTV was –13 mL (–37 to –3) and the median relative change in TTV was –64 % (–76 to –44).

3.3. Outcome parameters

After a median follow-up of 57 months (IQR, 43–65) in the CAIRO5 trial and 113 months in the external validation cohort (IQR, 78–130), approximately 80 % of patients had developed recurrence in both cohorts. Median RFS and OS in CAIRO5 were 7 months (95 % CI, 6–8) and 46 months (95 % CI, 41–58), respectively, compared to 9 months (7–13) and 57 months (33–125) in the validation cohort. The majority of first recurrence sites was confined to the liver only (Table 2). Other common sites of recurrence were the lungs, peritoneum, lymph nodes, bones, or at multiple sites.

3.4. Prognostic value of radiological parameters

In the CAIRO5 trial, after correcting for routinely measured clinicopathological variables, baseline TTV and absolute change in TTV were strongly prognostic in multivariable analyses for early recurrence ($P = 0.005$ and $P = 0.040$, respectively) and OS ($P = 0.024$ and $P = 0.006$). Absolute change in TTV was the strongest predictor for OS compared to all other prognostic variables in the model (Fig. 2).

In contrast, TBS did not show independent prognostic value in multivariable analyses for early recurrence (HR per 10 points increase, 1.05 [95 % CI, 0.38–2.90]; $P = 0.93$) and OS (HR, 0.35 [0.09–1.32]; $P = 0.11$). Similarly, RECIST1.1 was not a significant predictor in the CAIRO5 trial for either early recurrence (response vs stable vs progressive disease, ($P = 0.88$) or OS ($P = 0.35$).

In the external validation cohort, baseline TTV and absolute change in TTV were also independent predictors for both early recurrence ($P = 0.041$ and $P = 0.021$, respectively) and OS ($P < 0.0001$ and $P = 0.012$, respectively; Fig. 2). In the external validation cohort, TTV variables substantially improved the prognostic performance for OS when added to a model containing conventional prognostic factors

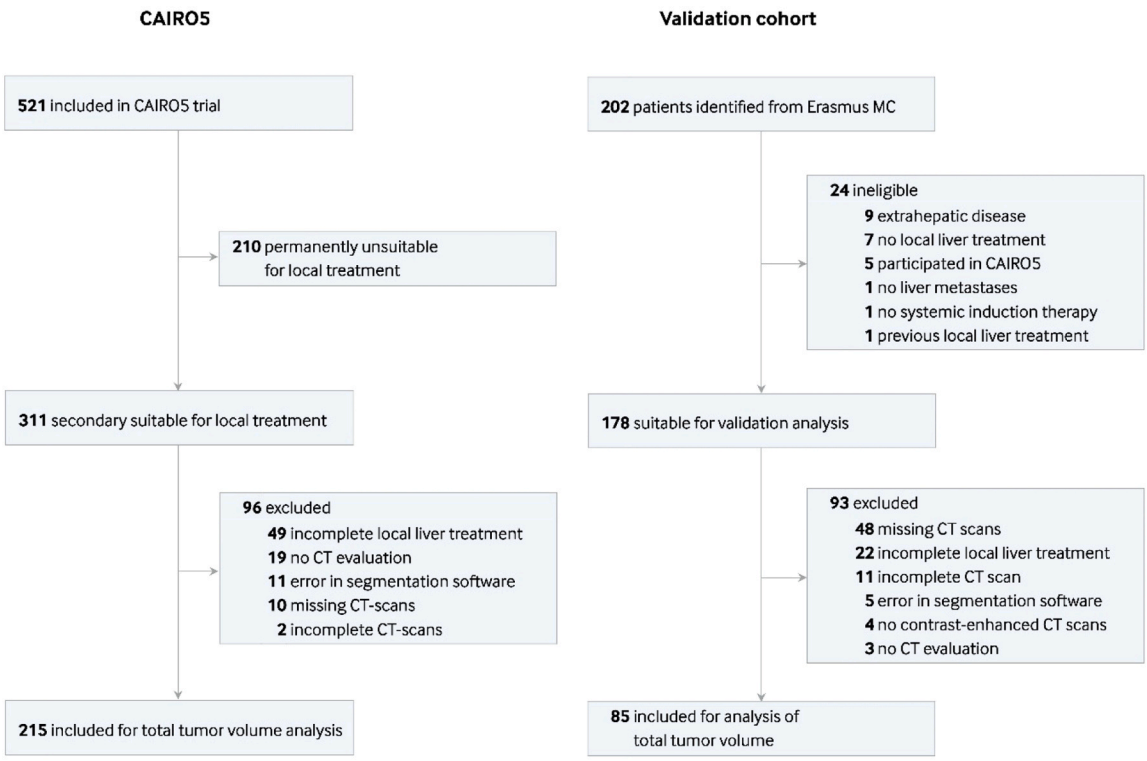

Fig. 1. Flow chart of patients included from the CAIRO5 trial and the external validation cohort.

(Harrell's *C*-statistic, 0.71 vs 0.65; difference [95 % CI], 0.06 [0.02–0.14]; P = 0.008).

There was substantial evidence for a nonlinear relationship between absolute change in TTV and early recurrence (nonlinearity test, P = 0.006) and OS (nonlinearity test, P = 0.009). The association between absolute change in TTV and early recurrence and OS is shown in Supplementary Fig. 1. Adjusted survival curves for a patient with a baseline TTV of 3 mL, 50 mL, and 300 mL are presented in Fig. 2E–F. The estimated 5-year overall survival probability at a baseline TTV of 3 mL, 50 mL, and 300 mL was 72 % (56–84 %), 37 % (29–47 %), and 7 % (1–28 %).

4. Discussion

This study demonstrated and validated for the first time that baseline TTV and absolute change in TTV following systemic therapy have substantial added prognostic value for early recurrence and OS in patients with initially unresectable CRLM who received systemic induction therapy, followed by complete local treatment of the liver metastases. In contrast, other size-based assessments such as RECIST1.1 and Tumor Burden Score did not show prognostic significance. In the external validation cohort, TTV variables remained the most prognostic variables for both early recurrence and OS.

In current clinical practice, conventional clinical data or proposed risk scores have been shown to be inadequate for predicting recurrence, timing of recurrence or survival probability after local treatment of with extensive CRLM [16]. For instance, in CAIRO5 patients who received local treatment, the C-statistic for the Fong- and GAME-scores were, respectively, 0.58 and 0.60 [20]. In this study, we did not compare the prognostic performance with these two scores, as the aim was to evaluate the prognostic value of TTV and not to develop and validate a prognostic prediction model for patients with CRLM.

By incorporating TTV in prognostic modeling, survival outcomes could be estimated more accurately. Patients with a high risk of early recurrence and/or mortality after local treatment can be withheld from invasive and burdensome local treatment options and palliative treatment options might be considered in an earlier stage for such patients. As a result, the addition of TTV in treatment-decision making could promote biologically driven surgery. Additionally, informing patients about the likelihood of recurrence and survival allows healthcare professionals to provide appropriate counseling. Incorporating other tumor markers, such as ctDNA, could further improve prognostication and patient counseling by better reflecting tumor biology. Our follow-up study will investigate this by also assessing ctDNA dynamics in blood samples from CAIRO5 patients.

For CRLM specifically, previous studies established the largest diameter and number of metastases as prognostic indicators for survival outcomes [21,30–32]. Our study demonstrates that TTV provided significant added value, even when accounting for the largest diameter and number of metastases. As such, the additional effort of TTV assessment is justified by the substantial added prognostic value of baseline TTV and absolute change in TTV.

Absolute change in TTV was the most prognostic variable for OS in CAIRO5, also after correcting for conventional prognostic variables, whereas RECIST1.1 did not show independent prognostic value for OS or early recurrence. These results suggest that absolute change in TTV could be a more sensitive endpoint for clinical trials than RECIST1.1, at least for patients with CRLM, but potentially also for other solid tumors. The validation of the RECIST1.1 criteria was based on the impact on response rate, but no research was done investigating the association with overall survival [33].

This study had several limitations. The present results were based on a selected group of patients with liver-only CRLM who underwent complete local treatment after induction with systemic therapy. Our findings will therefore be further investigated including patients who were not eligible for surgery after induction therapy or received incomplete local treatment. Additionally, the value of TTV as a tool for response evaluation to systemic treatment compared to the value of RECIST1.1 should be assessed, including re-evaluating the existing cutoff points. Lastly, TTV assessment relied on manual segmentations

Table 1
Baseline characteristics.

	CAIRO5 (n = 215)		EMC (n = 85)	
Age				
Median (IQR) – years	62	(54–70)	62	(54–67)
Age ≤ 70 years	167	(78)	72	(85)
Age > 70 years	48	(22)	13	(15)
Sex				
Male	136	(63)	57	(67)
Female	79	(37)	28	(33)
Baseline total tumor volume (mL)	48	(17–178)	28	(9–62)
Absolute change in total tumor volume (mL)	–22	(–81 to –6)	–13	(–37 to –3)
Relative change in total tumor volume (%)	–60	(–73 to –44)	–64	(–76 to –44)
Site of primary tumor				
Right colon	49	(23)	14	(16)
Left colon	84	(39)	34	(40)
Rectum	82	(38)	35	(41)
Double tumor	0	(0)	2	(2)
Time to metastases				
Synchronous	193	(90)	75	(88)
Metachronous	22	(10)	10	(12)
Mutation status				
RAS & BRAF wildtype	106	(49)	12	(14)
RAS (KRAS, NRAS) mutation	101	(47)	14	(16)
BRAF mutation	8	(4)	0	(0)
RAS + BRAF mutation	0	(0)	0	(0)
Missing	0	(0)	59	(69)
Serum CEA level				
Median (IQR) – µg/L	34	(9–139)	16	(5–42)
CEA ≤ 5 µg/l	36	(17)	24	(28)
CEA > 5 µg/l	179	(83)	61	(72)
Serum LDH level				
Median (IQR) – U/L	239	(192–332)		
LDH ≤ 225 U/L	96	(45)		
LDH > 225 U/L	119	(55)		
Number of metastases	9	(6–15)	4	(2–6)
Diameter of largest metastasis (mm)	35	(25–60)	35	(23–50)
Unilobar/bilobar distribution				
Unilobar	15	(7)	28	(33)
Bilobar	200	(93)	57	(67)

Data are presented as *n* (%) or median (interquartile range). Abbreviations: BRAF, v-Raf murine sarcoma viral oncogene homolog B; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase; RAS, rat sarcoma oncogene.

Table 2
Outcomes and treatment characteristics.

	CAIRO5 (n = 215)		EMC (n = 85)	
Outcomes				
Overall survival (months)	46	(28 to NA)	57	(33–125)
Recurrence-free survival (months)	7	(4–13)	9	(4–22)
Event				
Recurrence	178	(83)	63	(74)
Alive without recurrence	33	(15)	13	(15)
Death without recurrence	4	(2)	9	(11)
First site of recurrence, n (%)*				
Liver only	100	(56)	31	(49)
Lung only	22	(12)	7	(11)
Peritoneal only	7	(4)	3	(5)
Lymph node	6	(3)	4	(6)
Bone only	2	(1)	0	(0)
Other**	40	(23)	18	(29)
Treatment characteristics				
Systemic induction therapy				
Doublet chemotherapy + targeted therapy	148	(69)	17	(20)
Triplet chemotherapy + targeted therapy	67	(31)	2	(2)
Doublet chemotherapy	0	(0)	61	(72)
Other	0	(0)	5	(6)
Local treatment				
Surgery	103	(48)	35	(41)
Surgery + local ablative treatment/ radiotherapy	105	(49)	46	(54)
Local ablative treatment only	7	(3)	4	(5)
Liver resection				
Minor	112	(52)	55	(65)
Major	103	(48)	30	(35)
Resection margin				
R0	173	(81)	62	(73)
R1	35	(16)	18	(21)
Ablation only	7	(3)	5	(6)
pN status of the primary tumor				
Negative	21	(10)	28	(33)
Positive	49	(23)	48	(56)
No local treatment primary tumor	145	(67)	9	(11)
Stages local treatment				
One-stage	168	(78)	70	(82)
Two-stage	44	(20)	15	(18)
Three-stage	3	(1)	0	(0)
Postoperative chemotherapy				
Yes	92	(43)	2	(2)
No	123	(57)	83	(98)
RECIST 1.1				
Partial and complete response	154	(72)		
Stable disease	60	(28)		
Progression	1	(< 1)		
Tumor burden score				
Median (IQR)	11	(8–16)		
≤ 14.3	146	(68)		
> 14.3	69	(32)		
Treatment strategy				
Liver first	128	(60)	37	(44)
Primary tumor first	79	(37)	37	(44)
Synchronous local treatment primary tumor and liver metastases	8	(4)	11	(13)
Local treatment primary tumor				
Yes	173	(80)	78	(92)
No	42	(20)	7	(8)

Data are presented as *n* (%) or median (interquartile range). Abbreviations: RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1.
* Percentage shown with the total number of patients with recurrence (ie, 178 patients in CAIRO-5 and 63 in the validation cohort) defined as 100 %.
** Also includes multiple metastatic sites of recurrence.

from one radiologist using semi-automatic segmentation software. This is a time-consuming and tedious task, and is therefore not feasible to use in clinical practice compared to a fully automatic segmentation approach. As the successful implementation of TTV assessment in clinical practice necessitates the availability of a fully automatic segmentation model, our follow-up study will use a previously developed and validated automatic segmentation model that calculates TTV based on those segmentations [34].

In conclusion, baseline total tumor volume and change in total tumor volume after systemic therapy demonstrate strong, independent prognostic value for early recurrence and OS. Further validation is warranted, but the incorporation of TTV for patients with initially unresectable CRLM has the potential to enhance risk stratification and facilitate personalized clinical decision-making.

Ethical approval

The medical ethical committee approved this study, and due to the retrospective nature the need for informed consent was waived.

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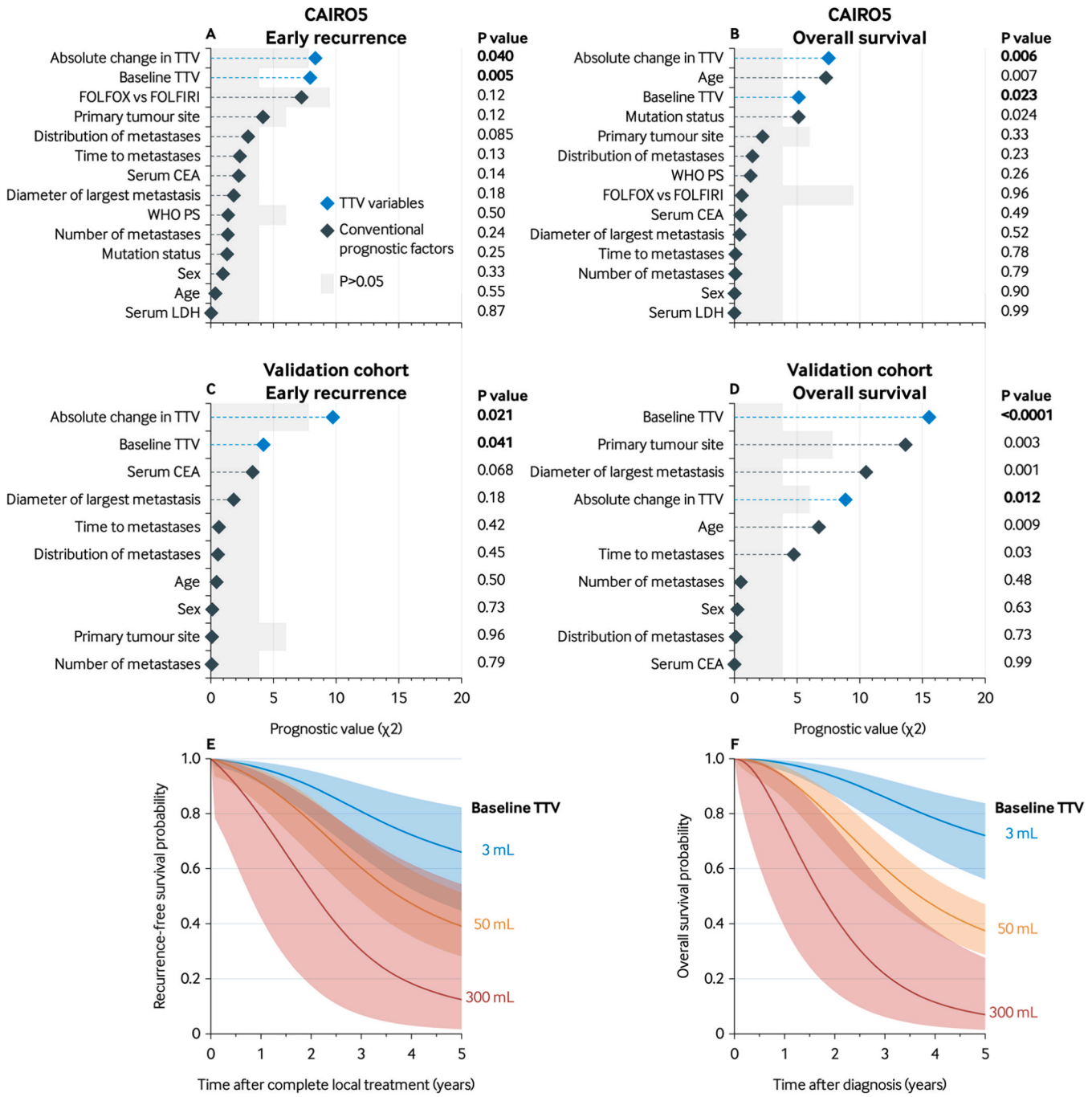

Fig. 2. Prognostic value of radiological total tumor volume. A–D, prognostic value (i.e., likelihood ratio χ^2) of baseline TTV, absolute change in TTV, and other prognostic variables in multivariable analyses for RFS and OS in the CAIRO5 trial and the external validation cohort. E–F, predicted survival curves for varying baseline TTV values in the validation cohort. Survival curves were estimated using a flexible parametric survival model, adjusted for all conventional prognostic factors (i.e., age, sex, serum CEA, number of metastases, distribution of metastases, time to metastases [synchronous vs metachronous], primary tumor site, and diameter of largest metastasis).

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors of this manuscript declare relationships with the following companies: C.J.A.P. has an advisory role for Nordic Pharma; SAS Analytics paid for traveling expenses G. Kazemier. This funding is not related to the current research. The remaining authors declare no potential conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114185.

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