A predictive model of polymetastatic disease from a multicenter large retrospectIve database on colorectal lung metastases treated with stereotactic ablative radiotherapy: The RED LaIT-SABR study

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A B S T R A C T

Aim: Stereotactic ablative radiotherapy (SABR) showed increasing survival in oligometastatic patients. Few studies actually depicted oligometastatic disease (OMD) evolution and which patient will remain disease-free and which will rapidly develop a polymetastatic disease (PMD) after SABR. Therefore, apart from the number of active metastases, there are no clues on which proven factor should be considered for prescribing local treatment in OMD. The study aims to identify predictive factors of polymetastatic evolution in lung oligometastatic colorectal cancer patients.

Methods: This international Ethical Committee approved trial (Prot. Negrar 2019-ZT) involved 23 Centers and 450 lung oligometastatic patients. Primary end-point was time to the polymetastatic conversion (tPMC). Additionally, oligometastases number and cumulative gross tumor volume (cumGTV) were used as combined predictive factors of tPMC. Oligometastases number was stratified as 1, 2–3, and 4–5; cumGTV was dichotomized to the value of 10 cc.

Results: The median tPMC in the overall population was 26 months. Population was classified in the following tPMC risk classes: low-risk (1–3 oligometastases and cumGTV $\leq$ 10 cc) with median tPMC of 35.1 months; intermediate-risk (1–3 oligometastases and cumGTV > 10 cc), with median tPMC of 13.9 months, and high-risk (4–5 oligometastases, any cumGTV) with median tPMC of 9.4 months (p = 0.000).

Conclusion: The present study identified predictive factors of polymetastatic evolution after SABR in lung oligometastatic colorectal cancer. The results demonstrated that the sole metastases number is not sufficient to define the OMD since patients defined oligometastatic from a *numerical* point of view might rapidly progress to PMD when the cumulative tumor volume is high. A tailored approach in SABR prescription should be pursued considering the expected disease evolution after SABR, with the aim to avoid unnecessary treatment and toxicity in those at high risk of polymetastatic spread, and maximize local treatment in those with a favorable disease evolution.

1. Introduction

The oligometastatic disease (OMD) is an intermediate state of metastatic disease characterized by a low metastatic burden amenable of local treatment, aiming to delay disease progression [1], systemic treatment change or extension [2], and finally improve overall survival (OS) or eventually cure [3]. The OMD is usually defined as having a maximum number of 3–5 simultaneous metastases [4]. Apart from the number of metastases that is actually-one of the main criteria for metastasis-directed therapies (MDT) prescription (i.e.: stereotactic ablative radiotherapy (SABR)), the OMD have a biological background that consider the inter-metastases and primary tumor cross-talk, as well as the metastasis-to-metastasis spread [5,6]. In this complex scenario, the aim of local treatment is reducing the likelihood of metastases to spread themselves co-operating with systemic drugs in controlling the onset of new metastatic foci.

Instead of being an *all-or-nothing* phenomenon, recent evidence suggest that the OMD is a complex clinical entity. In fact, in the clinical practice, OMD with apparently similar characteristics at presentation might have different clinical behavior [7]. Therefore, there is a clinical need for defining a model of disease progression useful to predict which patient might benefit from local treatments, maximizing its use in those patients clinically favorable or unable to receive systemic therapies and minimizing its use when a rapid metastatic spread is expected. In this context, the clinical benefit of MDT might be evaluated by the onset of the polymetastatic disease. The polymetastatic conversion permits to identify a change in the clinical behavior of the OMD to a state amenable of salvage systemic treatment only and with a limited role of local treatments [8]. Previously, in the LaIT-SABR study, a multicenter study on oligometastatic colorectal cancer, were identified several predictive factors of polymetastatic conversion [7]. Not only lesion number but also their dimension was identified as predictive factors, however their interplay in predicting the development of a polymetastatic disease was not explored.

The present is a secondary analysis of the LaIT-SABR study. The aim of the present study is to identify predictive factors of polymetastatic evolution in lung oligometastatic colorectal cancer patients to tailor SABR prescription.

2. Material and methods

2.1. Retrospective analysis overview

The present study is a subsequent analysis based on the previously published data of the LaIT-SABR study [7]. In the LaIT-SABR study [7] we analyzed the correlation between several biological, clinical, and dosimetrical factors and polymetastatic conversion (factors analyzed: BED, lesion diameter, mutational status of the primary tumor, previous systemic treatment, median SUVmax value, time to the OMD, primary tumor type, lesion site, and number of treated lung lesions). Among all the above reported variables evaluated by Cox regression multivariate analysis, only lesion diameter and lesion number (stratified as 1 versus 2–3 versus 4–5 metastases) were significantly associated with polymetastatic conversion. Therefore, only these two significantly correlated factors were chosen for the present analysis with the purpose of defining a model of polymetastatic conversion after SABR.

The present study was conducted on a multi-institutional, international, large retrospective database from 23 participating Centers including patients with lung oligometastases from colorectal cancer treated with SABR over the decade 2009–2019. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee (Prot. Negrar 2019-ZT).

Patients' data were anonymized and collected through an electronic CRF. Anonymized data were subsequently transferred for statistical analyses. The data in the database were validated to ensure the accuracy of the data entered. Required fields were specified to prevent missing data. The inclusion criteria for the present analysis were having received a SABR with a minimum BED of 100 Gy10 to all the treated metastases, and availability of, volume and survival data.

2.2. Study end-point, follow-up and statistics

The primary end-point was to evaluate the role of the oligometastases number and cumulative metastases volume in predicting the conversion to the polymetastatic disease. The time to the polymetastatic disease (tPMC) was defined as the time from the SABR start for the oligometastatic disease to the occurrence of >5 new metastases. Cumulative metastases volume (cumGTV) was the sum of the active treated

metastases in cc, and the number of treated metastases was stratified to 1, 2–3, and 4–5, as previously documented [7].

The follow-up up consisted of CT scan or FDG-PET CT each 3 months for the first two years of follow-up and each 6 months thereafter. The choose of the specific imaging technique during follow-up was at the discretion of each participating Center.

The univariate analyses for survival endpoints were performed with the Kaplan-Meier method. The log-rank test was applied to determine differences between the corresponding curves. Prognostic factors were evaluated for survival end-points as previously explained [7]. BED was calculated using an α/β ratio of 10 Gy. Cutoff Finder tool (http://molpath.charite.de/cutoff) was used to determine the optimal cumGTV cut-off defined as the value with the most significant split (log-rank test) (8). The Statistical analysis was performed using STATA V15 software (STATA Corp, College Station, TX). A p-value < 0.05 indicated a significant association.

3. Results

3.1. Patients' characteristics

The initial population consisted of 620 patients accounting for 1090 metastases. After data checking, 170 patients were excluded from the study due to the missing of required data, errors in data entry, or duplicate patients. The final population consisted of 450 patients and 705 metastases. The median age was 71 years (40–84). One-hundred six

Table 1
Patients' characteristics (n = 450) (%).

Mean age (range) (years)	71 (40–84)
Sex	
Male	156 (34)
Female	294 (66)
Primary site	
Colon	272 (60)
Rectum	178 (40)
Initial treatment	
Surgery	371 (82)
RCHT + surgery	68 (15)
Systemic therapy	11 (3)
Adjuvant chemotherapy	
Yes	114 (25)
No	324 (72)
Unknown	12 (3)
Histology	
Adenocarcinoma	429 (95)
Mucinous carcinoma	21 (5)
Initial stage	
Stage I	15 (3)
Stage II	94 (21)
Stage III	186 (41)
Stage IV	127 (28.5)
Unknown	28 (6.5)
Tumor mutations (%)	
EGFR	3.3
KRAS	22.6
NRAS	3
BRAF	1.76
MSI	0.44
Median time to OMD (range)	23.7 (0–126)
Systemic treatment before SABR	
Chemotherapy	249 (55.5)
TKI	4 (0.9)
Antiangiogenetic	32 (7)
Target therapy/immunotherapy	6 (1.3)
No	118 (26.3)
Unknown	41 (9)
Type of oligometastases	
Synchronous	106 (23.5)
Metachronous	344 (76.5)

RCHT: radiochemotherapy; OMD: oligometastatic disease: SBRT: stereotactic body radiotherapy; TKI: tyrosine-kinases inhibitor

(23.5 %) patients had synchronous metastases, while 344 (76.5 %) metachronous oligometastases. Patients' characteristics are reported in Table 1. Metastases number was distributed as follows: 1 oligometastasis 301 (67 %) patients, 2–3 oligometastases 120 (26 %) patients, and 4–5 oligometastases 29 (5.8 %) patients. The median cumGTV was 4.6 cc (0.2–255.8). The identified cumGTV cut-off for stratification analysis for single oligometastases cases was 10 cc. Treatment characteristics are reported in Table 2.

3.2. Time to polymetastatic conversion

The median tPMC in the overall population was 26 months (range 8.9–92.2 months). The median tPMC stratified for the number of oligometastases was: 27.7, 21.3, and 9.4 months for patients having 1, 2–3, and 4–5 metastases, with a 2-year tPMC of 56.5 %, 47.7 %, and 39.2 %, respectively (p = 0.005, Fig. 1a). The median tPMC stratified for cumGTV was 33.1, and 13.5 months for cumGTV $\leq$ 10 cc or >10 cc, with a 2-year tPMC of 57.9 %, and 37.5 %, respectively (p = 0.00, Fig. 1b).

By combining these 2 factors we identified 6 groups (see Table 3) and we analyzed the effect of different tumor volumes for each oligometastases strata. The median tPMC in the population with 1 metastasis was 36.1 and 13.9 months for patients having cumGTV $\leq$ 10 cc or > 10 cc, respectively, with a 2-year tPMC of 60.5 % and 41.3 %, respectively (p = 0.00, Fig. 2a). The median tPMC in the population with 2–3 oligometastases was 31.9 and 14.9 months for patients having cumGTV $\leq$ 10 cc or > 10 cc, respectively, with a 2-year tPMC of 54.1 % and 33.65 %, respectively (p = 0.058, Fig. 2b). The median tPMC in the population with 4–5 oligometastases was 6.7 and 9.4 months for patients having cumGTV $\leq$ 10 cc or >10 cc, respectively, with a 2-year tPMC of 30.3 % and 32.5 %, respectively (p = 0.85, Fig. 2c).

Therefore, we cross-compared group 1 (1 metastasis and cumGTV $\leq$ 10 cc) with group 3 (2–3 metastases and cum GTV $\leq$ 10 cc). The median tPMC was 36.1 and 31.9 months for group 1 and 3 respectively, with a 2-year tPMC of 60.5 % and 54.1 %, respectively (p = 0.12, Fig. 3a). Thereafter, we cross-compared group 2 (1 metastasis and cumGTV > 10 cc) with group 4 (2–3 metastases and cumGTV > 10 cc). The median tPMC was 13.9 and 14.9 months for group 2 and 4 respectively, with a 2-year tPMC of 41.3 % and 33.6 %, respectively (p = 0.89, Fig. 3b).

3.3. Risk class stratification

By combining the previous groups, we identified the following risk classes of polymetastatic conversion, defined as follows: low-risk (patients with 1–3 metastases and cumGTV $\leq$ 10 cc), intermediate-risk (patients with 1–3 metastases and cumGTV > 10 cc), and high-risk (4–5 metastases and any cumGTV). The median tPMC was 34.1, 13.9,

Table 2
Treatment characteristics (n = 705) (%).

Median lesion diameter (mm) (range)	14 (5–45)
Total treated lesions	
1	301 (42.5)
2	180 (25.5)
3	90 (13)
4	44 (6)
5	90 (13)
Median SUVmax (range)	4.9 (1–28)
Median total dose (Gy) (range)	48 (23–70)
Median dose per fraction (Gy) (range)	12 (5–30)
Median number of fractions (range)	3 (1–10)
Median BED (range)	125 (100–180)
Median GTV volume (cc) (per lesion)	3.07 (0.1–178)
Median cumulative GTV (cc)	4.6 (0.2–255.8)
Mean PTV volume (cc)	13.2 (1.2–113)
Lesion site	
Central	204 (29)
Peripheral	501 (71)

BED: biological effective dose; GTV: gross tumor volume; PTV: planning target volume
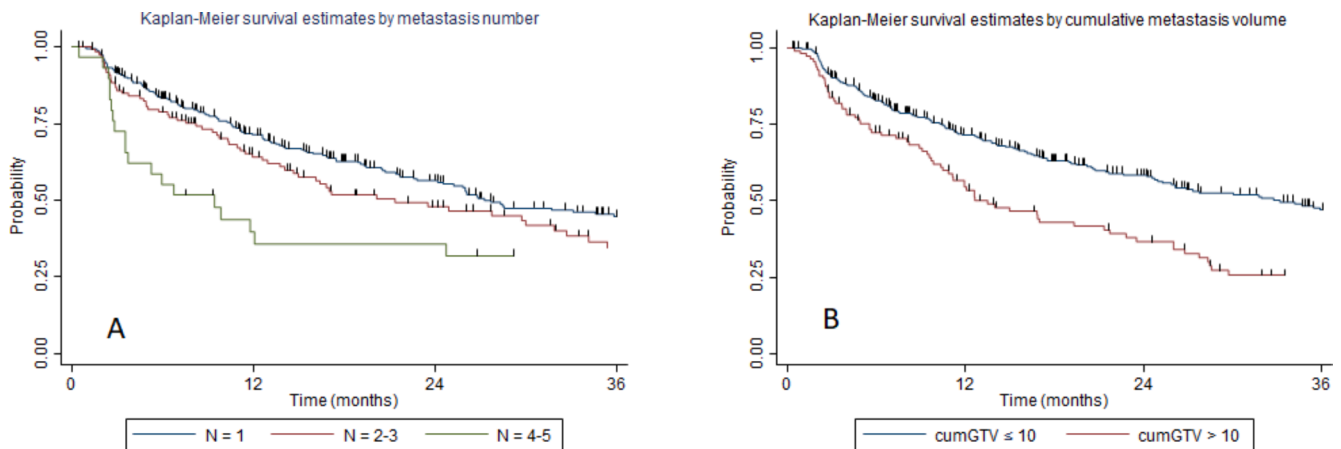
Fig. 1. Kaplan-Meier curve showing time to polymetastatic conversion stratified to: A) number of treated metastases; B) cumulative tumor volume.

Table 3
Analysis of time to polymetastatic conversion.

Covariates	Median tPMC (months)	P	Covariates	Median tPMC (months)	P
Number of oligometastases			Group 1: 1 oligometastasis and cumGTV < 10 cc	36.1	0.00
1	27.7	0.005	Group 2: 1 oligometastasis and cumGTV > 10 cc	13.9	
2–3	21.3		Group 3: 2–3 oligometastases and cumGTV < 10 cc	31.9	0.058
4–5	9.1		Group 4: 2–3 oligometastases and cumGTV > 10 cc	14.9	
			Group 5: 4–5 oligometastases and cumGTV < 10 cc	6.7	0.85
cumGTV			Group 6: 4–5 oligometastase and cumGTV > 10 cc	9.4	
<10 cc	33.1	0.00			
>10 cc	13.5				
tPMC: time ti polymetastatic conversion; cumGTV: cumulative gross tumor volume					

and 9.4 months for low, intermediate, and high-risk, respectively. The 2-year tPMC according to risk classification was 58.9 %, 38.4 %, and 35.3 % for low, intermediate, and high risk, respectively (p = 0.000, Fig. 3c) (Table 4).

4. Discussion

The actual criteria to define the oligometastatic disease are mainly based on the number of metastases and technical feasibility for SABR delivery, however as suggested by a recent ESTRO-ASTRO consensus on oligometastatic disease definition "there is no biological evidence supporting the maximal number of metastases, or the maximal lesion size, that can be treated to provide clinical benefit" [4]. In fact, several evidence demonstrated that despite being useful in clinical practice, lesion number is not fully representative of the complex scenario of the OMD. Patients with the same oligometastases *number* might both rapidly progress to the polymetastatic disease or maintain relatively long progression-free intervals [9,10]. This fact might suggest that other factors are involved in the disease progression.

Previously in the LaIT-SABR study [7], we demonstrated that also tumor dimension might influence the development of the polymetastatic disease, other than metastases number. In particular, patients with metastases diameter >20 mm and with more than three metastases had a significantly short tPMC. However, how these two factors interact with each other had not been explored. The present study identified predictive risk groups of polymetastatic progression in oligometastatic colorectal cancer.

The benefit of the addition of SABR to systemic treatment in the oligometastatic CRC is still a matter of debate. For example, the PulMICC trial explored the role of surgical metastasectomy in a series of CRC patients with lung oligometastases [11]. The study did not reach the expected accrual. Anyway, the study reported no survival benefit from the addition of surgery to the decisional workflow, questioning whether local treatment should be considered in this disease. On the other hand,

the CLOCC trial included patients with liver metastases from CRC treated with MDT plus systemic therapy [12]. The results showed that MDT addition significantly increased survival. Interestingly, the study included also patients with advanced liver disease, underlying in this way the need for identifying more accurate selection criteria for local treatment.

The majority of trials seem to demonstrate a global advantage when MDT is included in the management of OMD. For example, in the randomized phase II trial SABR-COMET [3], it was shown a significant survival advantage by the addition of SABR to systemic treatment in a series of 99 oligometastatic patients affected by different primary tumors (mainly NCLC, breast, prostate, and CRC) with a median survival of 50 versus 28 months [3] and a survival improvement of 13.6 % at 8 years of follow-up [13]. This trial is considered a milestone in the OMD treatment with SABR, however, it is a basket trial including different primary tumors that are commonly treated with different systemic treatments and consequently different survivals. By comparison, the phase III clinical trial SINDAS randomized untreated EGFR-mutated NSCLC patients to first-line tyrosine kinase inhibitor (TKI) or TKI plus SABR to all sites of disease. The preliminary results demonstrated a significant survival advantage favoring the experimental arm (median survival 25.5 months versus 17.4 months; HR 0.68, p = <0.001) [14]. On the other side, the phase II trial by Gomez et al. [15] randomized NSCLC patients (80 % of which harbored no mutation) with oligoresidual disease after primary chemotherapy to consolidative local therapy or observation. The results reported a significant OS improvement (secondary end-point) in the experimental arm (median 41.2 months versus 17 months). The median OS in the study by Klement et al. [16], which included oligometastatic CRC patients treated with SABR, was 27.9 months. Therefore, considering that different primary tumor has different disease progression timing and pattern, and different systemic treatment options (which may modify the disease course) it is reasonable that also disease-specific criteria should be considered for OMD definition and treatment.
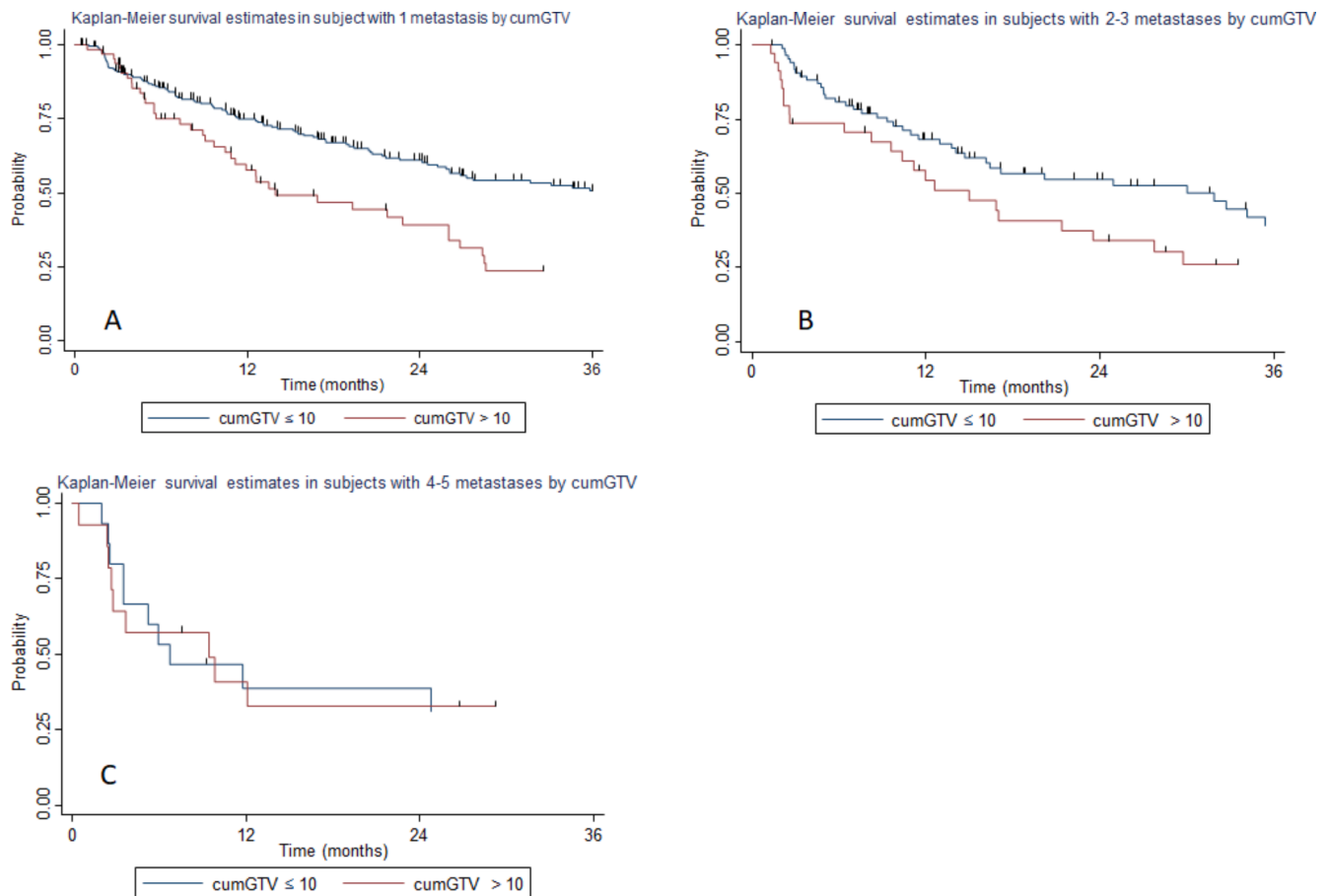
Fig. 2. Kaplan-Meier curve showing time to polymetastatic conversion of: A) patients with a single metastasis stratified to cumulative tumor volume (cumGTV); B) patients with 2–3 metastases stratified to cumGTV; C) patients with 4–5 metastases stratified to cumGTV.

In this context, Greco et al. demonstrated the possibility to stratify patients according to different factors other than metastases number [9]. Specifically, a combination of FDG-PET SUVmax and tumor volume could identify different patients' subgroups with different prognoses in a population of all-comer oligometastatic patients. In a study on oligo-metastatic prostate cancer patients, disease-free interval, site of metas-tases, and type of systemic therapy were significant predictors of polymetastatic conversion [17]. In the present study, a combined score of metastases number and total tumor volume allowed to identify-three risk classes. The low-risk population seems the most suitable for SABR, with a median tPMC of 34.1 months, while conversely, the most unfa-vorable subgroup seems the high-risk with 4–5 metastases and a median tPMC of 9.4 months. In this latter, local treatment could probably not significantly affect disease course and priority should be given to sys-temic treatment. On the other side, low-risk patients seem to benefit the most from SABR and they should be considered for local treatment, especially in patients not suitable for polychemotherapy or chemo-therapy at all. In the intermediate-risk patients, SABR alone could not be sufficient and should eventually be considered alongside chemotherapy.

Metastases volume has a direct connection to the metastatic poten-tial. In fact, growing metastases progressively secret pro-angiogenetic factors that increase vascular alteration and enhance permeability and anergic endothelial cells within the tumor. The poor vascular function recruit macrophages and neutrophils that further increase vascular permeability by the secretion of additional pro-angiogenic factors [6]. Larger lesions became also hypoxic and this can stimulate tumor inva-siveness [6]. Furthermore, growing metastases can release specific cy-tokines through the plasma or in platelets or microvesicles and can contribute to forming pre-metastatic niches which increase the

probability of metastases to spread themselves [5,6]. This biological background might justify our clinical finding and that the use of SABR in the early phase of the oligometastatic disease might shift the meta-statogenic equilibrium by reducing the probability of intra-metastatic spread [18].

This study is not without limitations. First of all, the analysis is based on a retrospective data collection, secondly, a proportion of patients was treated with SABR alone and this could have negatively impacted pol-ymetastatic spread. Points of strength are the large sample size, the homogeneity of patients' selection, and the use of high radiation doses. In conclusion, we developed a predictive model of polymetastatic dis-ease development considering metastases number and total tumor vol-ume. Different patient subgroups retain different clinical behavior and should be treated with a tailored approach.

5. Conclusion

The present is the largest series of colorectal oligometastatic patients and the first to identify a predictive model of polymetastatic spread in the specific setting of colorectal cancer. This model could be used in the clinical practice to improve SABR prescription and as a base stratifica-tion for future studies aiming to prospectively evaluate the role of SABR in oligometastatic colorectal cancer.

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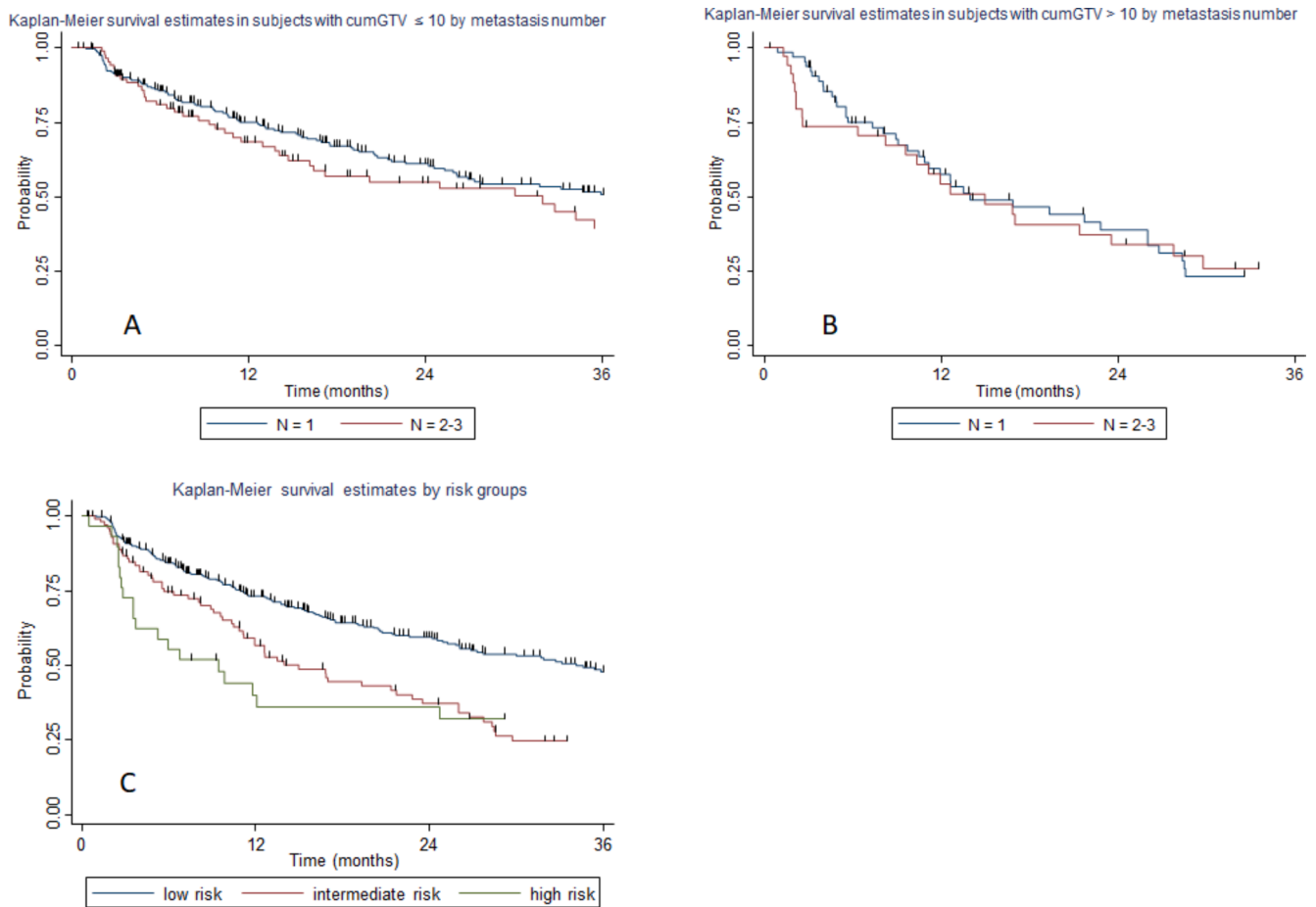
Fig. 3. Kaplan-Meier curve showing time to polymetastatic conversion of: A) patients with cumulative tumor volume (cumGTV) ≤ 10 cc stratified to number of oligometastases (1 versus 2–3); B) patients with cumGTV > 10 cc stratified to number of oligometastases (1 versus 2–3); C) risk classes stratification of poly-metastatic conversion.

Table 4
Risk class model (n = 450).

	Characteristics	Median tPMC	2-year tPMC
Low risk (323)	1–3 oligometastases and cumGTV < 10 cc	34.1	58.9 %
Intermediate risk (98)	1–3 oligometastases and cumGTV > 10 cc	13.9	38.4 %
High-risk (29)	4–5 oligometastases and any cumGTV	9.4	35.3 %

tPMC: time ti polymetastatic conversion; cumGTV: cumulative gross tumor volume

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.

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