Circannual variation of efficacy outcomes in patients with newly diagnosed metastatic colorectal cancer and treated with first-line chemotherapy

CIRCANNUAL VARIATION OF EFFICACY OUTCOMES IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC COLORECTAL CANCER AND TREATED WITH FIRST-LINE CHEMOTHERAPY

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ABSTRACT

Seasonal variation of baseline diagnosis (or clinical suspect) of stage I-III colorectal cancer patients has been repeatedly reported as an independent variable influencing overall survival. However, data are conflicting and no information is available about such a rhythm in advanced stage patients. To test whether a circannual rhythm of efficacy outcomes can be detected in this setting, we collected data about response rate (RR), progression free survival (PFS), and overall survival (OS) to first-line chemotherapy of 1610 newly diagnosed metastatic patients treated at four independent centers. Responses to first-line chemotherapy were available for 1495 patients. A strong circannual rhythm in RR was evident, with the higher proportion of responding patients in the subgroup diagnosed in January (acrophase). At the time of data cut-off, 1322 patients progressed and 986 died, with median PFS and OS of 11 and 25.6 months, respectively. A circannual rhythmicity of the proportion of patients progressing at 6 months and surviving at 1 year was demonstrated, with acrophases located both in winter (February and January, respectively), similarly to what reported for RR. Several interpretations about the genesis of this cyclic variation could be claimed: the rhythm in sunlight exposure and, as a consequence, of vitamin D serum levels and folate degradation, the variability in toxic effect intensity of chemotherapy, and the rhythm in the biological behavior of tumor cells. This observation is worth of further investigation both in preclinical and clinical settings in order to better elucidate the underlying mechanisms.

Key words: colorectal cancer; circannual rhythms, first-line chemotherapy

INTRODUCTION

There is a growing body of evidence that the season of baseline diagnosis may affect survival of patients with different solid tumors, including breast and colorectal cancer (CRC). Available data, mainly from large epidemiological studies, are conflicting with some studies reporting better survival for those patients diagnosed in summertime (Mason BH et al., 1990; Robsahm TE et al., 2004), while another paper supported the alternative hypothesis (Joensuu H & Toikkanen S, 1991) and finally an additional study that did not show any seasonal variation (Galea MH & Blamey RW, 1991). More specifically, a Norwegian study reported an increased death risk in patients bearing stage I-III CRC diagnosed in wintertime (Moan J et al., 2010), whereas a Finnish study in the same disease setting demonstrated a worse prognosis for patients diagnosed in summertime (Sankila R et al., 1993).

Possible explanations for this variability in survival claim for the circannual rhythm of sun exposure and consequently of serum vitamin D levels, but the existence of conflicting data may argue in favour of potential confounding factors. For instance, the efficacy of adjuvant and subsequently of palliative chemotherapy at the time of the recurrence of the disease, both affecting overall survival, might be dependent from the presence of a plausible circannual rhythmicity in tumour aggressiveness and chemosensitivity.

The issue remains largely unexplored and consequently through a large multi-institutional retrospective database we aimed to investigate whether the clinical outcomes of patients with advanced CRC treated with first-line chemotherapy showed a rhythmical circannual variation according to the month of baseline diagnosis of metastatic disease.

PATIENTS AND METHODS

Patients

From 1996 up to 2013 data about clinical characteristics and outcomes of consecutive CRC patients diagnosed and treated for metastatic disease in four Italian institutions (University of Torino, Oncologia Medica, AOU San Luigi di Orbassano; University of Torino, IRCCS Candiolo; University of Oriental Piedmont, AOU Maggiore della Carità, Novara; and Colorectal Cancer Unit, AOU Città della Salute, Torino) have been included in a clinical database including the following variables: patients' clinical and pathological characteristics, date of diagnosis and sites of first distant metastasis, date of first progression, chemotherapy history (if any), efficacy outcomes including disease free interval, date of death or last follow-up visit. Date of diagnosis was defined as the date of the first appearance of a metastasis in patients with metachronous disease, whereas it was the date of surgical intervention in resected patients or the date of colonoscopy in patients with synchronous disease. Chemotherapy was started within 4 and 6 weeks from diagnosis in non-surgical and surgical patients, respectively. Patients received first-line chemotherapy according to each institution protocol and for a minimum period of time of at least 6 months, unless otherwise contraindicated. The Institutional Review Boards of the participating Centres approved data collection.

Outcomes evaluation

Treatment response was classified according to the UICC criteria (Miller AB et al., 1981) up to 2001, and then according to RECIST criteria (Eisenhauer EA et al., 2009). Complete response (CR) was defined as the complete disappearance of all clinically detectable malignant disease. As far as the UICC criteria is concerned, a partial response (PR) was characterized as a decrease >50% in the sum of the products of the two longest perpendicular diameters of all measurable lesions and a progressive disease (PD) was defined as an increase of at least 25% in the size of measurable lesions and the development of new lesions. According to the RECIST criteria, the definition of PR

and PD are a decrease >30% and an increase >20% of the sum of the longest diameters of the target lesions, respectively. Only the best tumor response was recorded.

Progression free survival (PFS) and overall survival (OS) were estimated from the start of first-line treatment until disease progression or death or date of the last follow-up. The cut-off date for statistics computation was December 1st, 2014. Patients not progressing or alive or lost to follow-up at the time of data computation were censored at the time of the last follow-up examination.

Statistical analyses

Survival curves, proportion of patient at risk of progression at 6 months and at risk of death at one year were calculated and plotted using the Kaplan-Meier method and validated using the log-rank test. Differences between proportions were validated by the Chi-Square test, with Yates' correction when necessary. Non-parametric variables were analyzed using the Mann-U-Whitney test, whereas the parametric variables by the t-test for means. Rhythms were characterized and validated by two-way ANOVA and by COSINOR analysis (Halberg F, 1969). In the COSINOR analysis, a predetermined period (τ=24 h) is fitted to the cosine curves ($yi=M+A \cos(\Phi+\theta\tau i)+ei$) and their significance is evaluated by the least-square method. This analysis yields three main parameters: MESOR (M, Midline Estimating Statistics Of the Rhythm of the fitted cosine curve); acrophase (Φ, occurrence of maxima in hours, which may not take place at the time during which maximum concentration was observed); and double amplitude (2A, the difference between the highest and lowest point of the fitted cosine curve). Correlation coefficient constant and mean square error determine the goodness-of-fit of the cosine curve.

These statistical computations were performed using the SPSS for Windows and STATISTICA for Windows software.

RESULTS

Patients

A total of 1610 patients were included in the study and patients' characteristics are summarized in Table 1. Median age was 63.7 years (range 26.8-89.5). Males were predominant (963 patients, 59.8%), most of the patients presented with synchronous metastases (898 patients, 55.8%), and the primary tumors were mainly located in the colon (1137 patients, 70.6%). The majority of metastatic lesions were detected in the liver (68.6%), followed by lung (26.3%). Characteristics of the patients according to centers were well balanced with no statistically significant differences in the proportion of liver or lung involvement, of synchronous or metachronous metastases, gender, performance status, grading, stage at diagnosis (Chi-Square p values for all these comparisons >0.05), and age (t-test p=0.54). The highest and the least number of diagnosis were recorded in April (164) and in September (105), respectively. There was no difference in the number of patients stratified according to the month of diagnosis and to centers (two way ANOVA F=0.621, DF=33, p=0.95).

Response Rate

Response rate to first line chemotherapy was available for 1495 patients (92.9%): 580 at center 1 (96.5%); 535 at center 2 (99.1%); 247 at center 3 (91.5%); and 133 at center 4 (66.8%). Sixty-three patients did not receive chemotherapy due to age and/or to concomitant chronic co-morbidities, while information about objective response was missed in 52 patients (3.2%). Overall, partial or complete response was documented in 577 patients (38.6%). Response rate according to the month of diagnosis is summarized in Figure 1. The highest tumor response rate (46.1%) was evident in patients diagnosed with metastatic disease on January, whereas the least response rate (27.3%) was recorded in the group diagnosed on August. An evident circannual variation of this outcome was validated by COSINOR analysis (Fig. 2) with a MESOR of 37.7%, double amplitude of 11.1% and acrophase in January ($p<0.001$). The circannual rhythmicity was evident in all centers (Table 2), with superimposable MESORs and acrophases in winter. Similar rhythms were reported for patients

stratified according to gender (Table 2) (ANOVA p=0.8). A non statistically significant trend for a lower response rate and a delayed acrophase was reported in older patients (ANOVA p=0.14). Finally, it was not possible to demonstrate a circannual variation in response rates in patients with PS>0.

Time to progressive disease

At the data cut-off of December 1, 2014 a total of 1322 patients already progressed (82.1%). Data on tumor progression after first-line chemotherapy were not available for the 63 patients not treated, and in 12 patients for whom any information about chemotherapy was lacking. Two hundred and thirteen patients did not progressed at the time of data analysis or were lost to follow-up.

Median overall progression free survival (PFS) was 11.0 months. Median PFS for each center were 11.2, 10.3, 12.5, and 10.0 respectively (p=ns).

The proportion of patients not having progressed at 6 months after the beginning of chemotherapy stratified according to the month of diagnosis of metastatic disease presented a significant circannual variation (Fig. 3) validated by the COSINOR analysis. Characteristics of the curve were as follows: MESOR 79%, double amplitude 5.2% and acrophase in the month of February (p<0.001). COSINOR analyses for each center are summarized in Table 2. Circannual variations were evident for centres 1, 3, and 4, but not for centre 2. A general acrophase concordance was reported in winter. No difference in circannual rhythms was evident in patients stratified according to gender, age and PS (Table 3).

Overall survival

At the time of data analysis, 986 (61.2%) patients died, with a median follow-up of 21.4 months. Overall median survival of the entire population was 26.5 months and the proportion of surviving patients at one year was 80.9%. Median overall survival time (OS) for each center was: 23.0, 26.7, 31.3, and 27.7 months, respectively (p<0.001). A significant variation according to a circannual

pattern was evident (Fig. 4), with a MESOR of 80.0%, double amplitude of 4.2% and the acrophase in January (p=0.05). COSINOR analysis validated rhythmicity of centers 1 and 3 (Table 2). In these two centers, the highest proportion of surviving patients at one year was recorded for those diagnosed in January. No difference in circannual rhythms was evident in patients stratified according to gender, age and PS (Table 3).

Dose of 5-FU delivered to patients

The total dose of 5-FU administered to patients during first line chemotherapy was elaborated in center 1, were data were available for 588 patients. Median 5-FU dose (range) was 32,500 (2,000-94,800) mg/sqm. COSINOR analysis confirmed a circannual rhythmicity in the dose administered with MESOR=32,217 mg/sqm, double amplitude of 3,250 mg/sqm and the acrophase in January (p= 0.05). A circannual rhythm was also demonstrated when considering 5FU dose intensity, with MESOR of 1,512 mg/sqm/week, double amplitude of 174 mg/sqm/week, and acrophase in February ($p<0.001$).

DISCUSSION

This is the first report showing a circannual variation of the activity and efficacy of first-line chemotherapy in terms of response rate, progression free survival and overall survival in patients with metastatic colorectal carcinoma, with best outcomes recorded in patients diagnosed in winter.

Chronobiological studies are difficult to carry on in clinical settings especially because large numbers are required. We then planned to collect data from four independent institutions managing metastatic colorectal cancer patients. Distribution of the patients was homogeneous with no major differences demonstrated. Even though a lower number of patients were diagnosed in August (i.e. the month traditionally dedicated to vacation in Italy), no difference in the incidence of diagnosis between months and centers was evident. The great majority of the patients received an oxaliplatin-

or irinotecan- containing first line chemotherapy which have been demonstrated to be superimposable in determining patient outcome (Tournigand C et al., 2004).

Our data clearly showed a robust circannual rhythm of antitumor drug activity, with best response rates in patients diagnosed in winter. This circannual pattern was demonstrated in all the four centers participating in the study representing an internal validation of the results. Differences in MESOR and Double Amplitude of Center 4 could be explained by the lower patient sample which magnifies statistical errors. Similar rhythmic variations were demonstrated for patients stratified according to gender, whereas no rhythms and lower response rates were recorded in older and in symptomatic patients (PS>0). This is in line with what already published in these latter patient subgroups (Campos Costa I et al. 2013; Pugliese P et al. 2002). The circadian variation in response rate was further validated by the presence of a synchronized rhythm for progression free survival rate at six months. No differences were shown when patients were stratified according to gender, age or PS. The absence of such a rhythm in one center could be explained by chance or by institutional differences in determining tumor progression that may have smoothened variability as demonstrated by its double amplitude of only 7%. As far as the circannual variation in survival rate at one year is concerned, an overall rhythm has been demonstrated with the best survival rate shown for those patients diagnosed in winter, further confirming the evidence that patients diagnosed between December and February are those having the best outcomes. Survival rhythm, however, is fair less definitive as demonstrated by the results stratified according to centers. This may be due to differences in second and third line treatments that have been shown to affect overall survival (Heinemann V et al., 2014). This possible explanation is further supported by the statistically validated differences in median OS that we observed between centers.

Differences in OS according to the season of diagnosis have been shown for several tumors (Mason BH et al., 1990; Robsahm TE et al., 2004; Joensuu H & Toikkanen S, 1991), and particularly for colorectal cancer patients. A potential explanation claims for the circannual variations of sun exposure and consequently, of the circulating vitamin D serum levels. In fact, since the beginning of

2000s, it was proposed that vitamin D is a protective factor against colorectal cancer (Garland CF & Garland FC, 2006). This hypothesis arose from the analysis of the geographic distribution of colon cancer deaths in the US, that were higher in areas where people were exposed to inferior amounts of natural light such as in the larger cities and rural areas at high latitudes. The hypothesis was also supported by a comparison of colon cancer mortality rates in areas that vary in mean daily solar radiation penetrating the atmosphere (Borisenkov MF., 2011). The relationship between vitamin D levels and patient outcomes was recently confirmed in a prospective study involving 1598 Scottish patients with stage I-III CRC, where high pre-surgery vitamin D levels was associated to a longer OS (Zgaga L et al., 2014). However, this hypothetical explanation hardly fit with our observation. In fact, nearly 82% of metastatic CRC patients are vitamin D insufficient (Ng K, 2011; Zgaga L et al., 2014) and thus the presence of a circannual rhythm is at least questionable. Moreover, patients submitted to 5FU chemotherapy are asked to limit sun exposure in order to reduce skin toxicities. The highest progression rate shown in those patients diagnosed in August (Fig. 1) could rather suggest an inverse relationship between vitamin D level and response to chemotherapy, contrasting with what above reported. Indeed, our data cannot be completely compared to what already published (Mason BH et al., 1990; Robsahm TE et al., 2004; Joensuu H & Toikkanen S, 1991; Galea MH & Blamey RW, 1991; Moan J et al., 2010; Sankila R et al., 1993), as we took into account metastatic patients instead of completely resected patients, and then specific investigations should be conducted.

Another potential explanation rely on the onset of toxicities such as diarrhea and vomiting that may lead to a dehydration status more often in summer than in winter due to weather condition. In fact, median summer temperature in Northern Italy raises 30°C. As a consequence, patients diagnosed in summer and with chemotherapy start during the hottest months of the year are those that had more dose reductions and thus a low drug dose-intensity. In center 1, where data were available, we demonstrated a circannual rhythm in the total dose of 5FU administered to patients, with the acrophase in the month of January, and in 5FU dose intensity, with the acrophase in the month of

February, confirming the hypothesis. This may have influenced our observation as it has been repeatedly demonstrated that there is a direct correlation between the total dose of 5-FU administered and the treatment outcome (Garufi C et al. 1997; Gamelin EC1, Danquechin-Dorval EM, Dumesnil YF, Maillart PJ, Goudier MJ, Burtin PC, Delva RG, Lortholary AH, Gesta PH, Larra FG. Relationship between 5-fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. Cancer. 1996 Feb 1;77(3):441-51).

Another intriguing hypothesis that may explain these discrepancies in outcomes comes from Norwegian researchers (Steindal AH et al., 2007). These Authors postulated that the folate degradation induced by UV exposure could be one of the potential causes of the observed differences in survival among resected cancer patients. This intriguing theory raises another important issue worth of discussion. Because folate is a modulator of 5-fluorouracil (5-FU) antitumor activity, its putative degradation by UV may reduce drug efficacy.

Finally, it has been shown a circannual variation in tumor cell proliferation in non-Hodgkin's lymphomas (Smaaland R et al, 1993) and in thyroid tumors (Akslen LA & Sothern RB, 1998), with acrophases in winter for both studies. Consequently, we may further hypothesize that chemotherapy is more active in wintertime as tumor cells are more proliferating.

In conclusion, we showed for the first time a circannual variation of outcomes in patients diagnosed with metastatic colorectal cancer and treated with first line chemotherapy. Best response rate, progression free survival and overall survival rates were recorded in patients diagnosed in winter.

AKNOLEDGEMENTS

Authors disclose any potential conflict of interest.

FIGURE LEGENDS

Figure 1. Responses to first line chemotherapy according to the month of diagnosis of metastatic disease (PD: progressive disease: SD: stable disease: Resp: response).

Figure 2. COSINOR analysis of response rate according to months of diagnosis of metastatic disease (MESOR=37.7%; 2A=11.1%; Acrophase=January. P<.001).

Figure 3. COSINOR analysis of the probability of progression at 6 months according to months of diagnosis of metastatic disease (MESOR=79%; 2A=5.2%; Acrophase=February. P<.001).

Figure 4. COSINOR analysis of survival probability at 1 year according to month of diagnosis of metastatic disease (MESOR=80%; 2A=4.2%; Acrophase=January. p=.05).

Table 1. Characteristics of the patients included in the study

	Total	**Center 1**	**Center 2**	**Center 3**	**Center 4**
Number of patients (%)	1610	601 (37.3)	540 (33.5)	270 (16.8)	199 (12.4)
Male (%) Female (%)	963 (59.8) 647 (40.2)	371 (61.7) 230 (38.3)	311 (57.6) 229 (42.4)	166 (61.5) 104 (38.5)	115 (57.8) 84 (42.2)
Median age at diagnosis years (range)	63.7 (26.8-89.5)	62.8 (28.9-82.9)	62.5 (26.8-84.9)	65.5 (29.6-87.4)	68.9 (32.9-89.5)
Characteristics of primary					
Stage at diagnosis (%) I II III IV Unknown	 13 (0.8) 194 (12.0) 433 (26.9) 898 (55.8) 72 (4.5)	 4 (0.7) 75 (12.5) 148 (24.6) 372 (61.9) 2 (0.3)	 2 (0.4) 61 (11.3) 126 (23.3) 293 (54.3) 58 (10.7)	 1 (0.4) 40 (14.8) 89 (33.0) 129 (47.8) 11 (4.0)	 6 (3.0) 18 (9.0) 70 (35.2) 104 (52.3) 1 (0.5)
Site of primary (%) Colon Rectum Unknown	 1137 (70.6) 421 (26.1) 52 (3.3)	 429 (71.4) 170 (28.3) 2 (0.3)	 380 (70.4) 112 (20.7) 48 (8.9)	 181 (67.0) 88 (32.6) 1 (0.4)	 147 (73.9) 51 (25.6) 1 (0.5)
Grading (%) 1 2 3 Unknown	 32 (2.0) 726 (45.1) 342 (21.2) 510 (31.7)	 13 (2.2) 308 (51.2) 146 (24.3) 134 (22.3)	 7 (1.3) 138 (25.6) 101 (18.7) 294 (54.4)	 5 (1.9) 173 (64.1) 56 (20.7) 36 (13.3)	 7 (3.5) 107 (53.8) 39 (19.6) 46 (23.1)
Months of diagnosis of metastatic disease - No. of patients (%)					
January	134 (8.3)	44 (7.3)	46 (8.5)	27 (10.0)	17 (8.5)
February	124 (7.7)	46 (7.6)	33 (6.1)	19 (7.0)	26 (13.1)
March	150 (9.3)	64 (10.6)	39 (7.2)	20 (7.4)	27 (13.6)
April	164 (10.2)	64 (10.6)	55 (10.2)	23 (8.5)	22 (11.1)
May	152 (9.4)	63 (10.5)	36 (6.8)	32 (11.9)	21 (10.6)
June	132 (8.2)	39 (6.6)	58 (10.7)	23 (8.5)	12 (6.0)
July	135 (8.4)	44 (7.3)	54 (10.0)	25 (9.3)	12 (6.0)
August	110 (6.8)	42 (7.0)	41 (7.6)	15 (5.6)	12 (6.0)
September	105 (6.6)	44 (7.3)	32 (5.9)	20 (7.4)	9 (4.5)
October	144 (8.9)	54 (9.0)	53 (9.8)	27 (10.0)	10 (5.0)
November	118 (7.3)	42 (7.0)	46 (8.5)	18 (6.7)	12 (6.0)
December	142 (8.9)	55 (9.2)	47 (8.7)	21 (7.7)	19 (9.6)
Metastases (%) Synchronous Metachronous Unknown	 767 (47.6) 795 (49.4) 48 (3.0)	 259 (43.1) 342 (56.9) 0 (0)	 285 (52.8) 207 (38.3) 48 (8.9)	 124 (45.9) 146 (54.1) 0 (0)	 99 (49.8) 100 (50.2) 0 (0)
Median Disease Free Interval (Range)	11.4 mo (1-217.7)	8.2 (1-217.7)	17.2 (1-103.7)	10.3 (1-138.9)	13.0 (1-102.5)
Site of metastasis (%)					
Liver	1105 (68.6)	419 (69.7)	373 (69.1)	183 (67.8)	130 (65.3)
Lung	423 (26.3)	158 (26.3)	104 (19.3)	103 (38.1)	58 (29.1)
Local	238 (14.8)	79 (13.1)	68 (12.6)	42 (15.6)	49 (24.6)
Other (Peritoneum,	377 (23.4)	142 (23.6)	120 (22.2)	66 (24.4)	49 (24.6)

Ovary, etc)					
Performance Status at study entry (%) 0 1-2 3-4 Unknown	 639 (39.7) 449 (27.9) 16 (1.0) 506 (31.5)	 238 (39.6) 245 (40.8) 8 (1.3) 110 (18.3)	 133 (24.6) 61 (11.3) 0 (0) 346 (64.1)	 205 (75.9) 61 (22.6) 1 (0.4) 3 (1.1)	 63 (31.7) 82 (41.2) 7 (3.5) 47 (23.6)
Chemotherapy (%)					
5FU based	394 (24.5)	181 (30.1)	89 (16.5)	95 (35.2)	29 (14.6)
5FU + Oxaliplatin based	861 (53.5)	375 (62.4)	327 (60.6)	101 (37.4)	58 (29.1)
5FU + Irinotecan based	154 (9.6)	9 (1.5)	99 (18.3)	22 (8.1)	24 (12.1)
5FU + Oxaliplatin + Irinotecan based	9 (0.6)	0 (0)	2 (0.4)	5 (1.9)	2 (1.0)
Chemotherapy + Biologicals	77 (4.8)	15 (2.5)	18 (3.3)	24 (8.9)	20 (10.1)
Unknown or not administered	115 (7.0)	21 (3.5)	5 (0.9)	23 (8.5)	66 (33.1)
No of patients progressed	1322 (82.1)	521 (86.7)	487 (90.2)	191 (70.7)	123 (61.8)
No of patients censored for progression	213 (13.2)	80 (23.3)	53 (9.8)	79 (29.3)	1 (0.5)
No of patients without progression data	75 (4.7)				75 (37.7)
Overall Progression Free Survival (months; median - quartiles)	11.0 (6.8-16.7)	11.2 (6.3-17.8)	10.3 (7.0–16.0)	12.5 (8.1-18.9)	10 (6.7-13.4)
No of patient died	986 (61.2)	454 (75.5)	382 (71.3)	119 (44.1)	31 (15.6)
No of patient censored for survival	624 (38.8)	147 (24.5)	158 (28.7)	151 (55.9)	168 (84.4)
Overall Survival (months; median - quartiles)	26.5 (14.5-48.1)	23.0 (11.6-39.7)	26.7 (15.2-54.6)	31.3 (18.1-51.1)	27.7+

Table 2. COSINOR Analyses of circannual rhythmicity of outcomes according to the month of diagnosis of metastatic disease stratified according to center

Response rate (%)				
	MESOR	**Double Amplitude**	**Acrophase**	**p**
Center 1	35.7	14.8	December	<.0001
Center 2	45.0	4.2	March	=.03
Center 3	34.5	17.8	December	=.01
Center 4	27.4	33.1	February	<.001
Overall	*37.7*	*11.1*	*January*	*<.001*

Patients at risk of progression at 6 months (%)				
	MESOR	**Double Amplitude**	**Acrophase**	**p**
Center 1	73.4	10.8	January	<.0001
Center 2	79.9	7.0	June	ns
Center 3	78.1	19.0	February	<.001
Center 4	69.8	20.0	December	<.001
Overall	*79.0*	*5.2*	*February*	*<.001*
Survival rates at 1 year (%)				
	MESOR	**Double Amplitude**	**Acrophase**	**p**
Center 1	72.4	8.4	January	<.01
Center 2	81.7	3.8	April	ns
Center 3	79.4	9.6	January	=.06
Center 4	79.8	6.8	September	ns
Overall	*80.0*	*4.2*	*January*	*=.05*

Table 3. COSINOR Analyses of circannual rhythmicity of outcomes according to the month of diagnosis for patients stratified according to main characteristics at diagnosis of metastatic disease.

Response rate (%)					
	MESOR	**Double Amplitude**	**Acrophase**	**COSINOR p**	**ANOVA p**
Male	38.3	12.7	December	<.0001	.80
Female	38.5	12.8	February	<.01	
Age >70	28.9	16.0	March	.15	.14
Age <70	40.4	10.0	December	<.0001	
PS 0	42.4	10.2	February	<.001	<.001
PS 1-2	27.1	9.8	December	0.20	
Patients at risk of progression at 6 months (%)					
	MESOR	**Double Amplitude**	**Acrophase**		
Male	79.1	3.6	February	.05	.76
Female	76.5	9.8	February	<.001	
Age >70	71.5	8.0	February	.05	.74
Age <70	79.3	8.6	February	<.001	
PS 0	84.7	8.8	February	<.001	.50
PS 1-2	70.1	12.4	February	.05	
Survival rates at 1 year (%)					
	MESOR	**Double Amplitude**	**Acrophase**		
Male	78.2	2.6	November	0.1	.06
Female	80.4	8.9	February	<.001	
Age >70	74.6	9.0	March	.04	.66
Age <70	80.4	6.4	January	.05	

PS 0	85.1	7.2	December	.1	.19
PS 1-2	68.4	8.6	March	.1	

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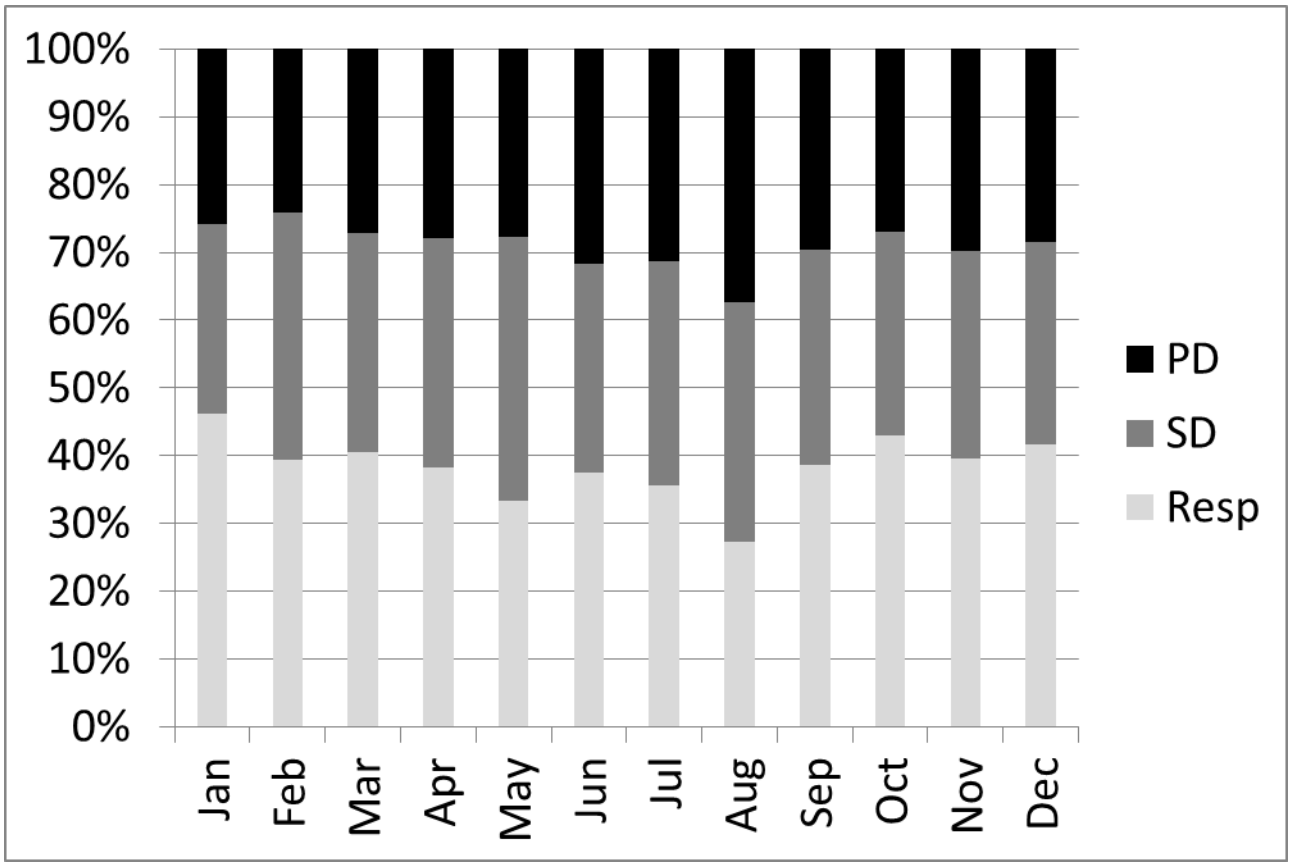
100%
90%
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Figure 1

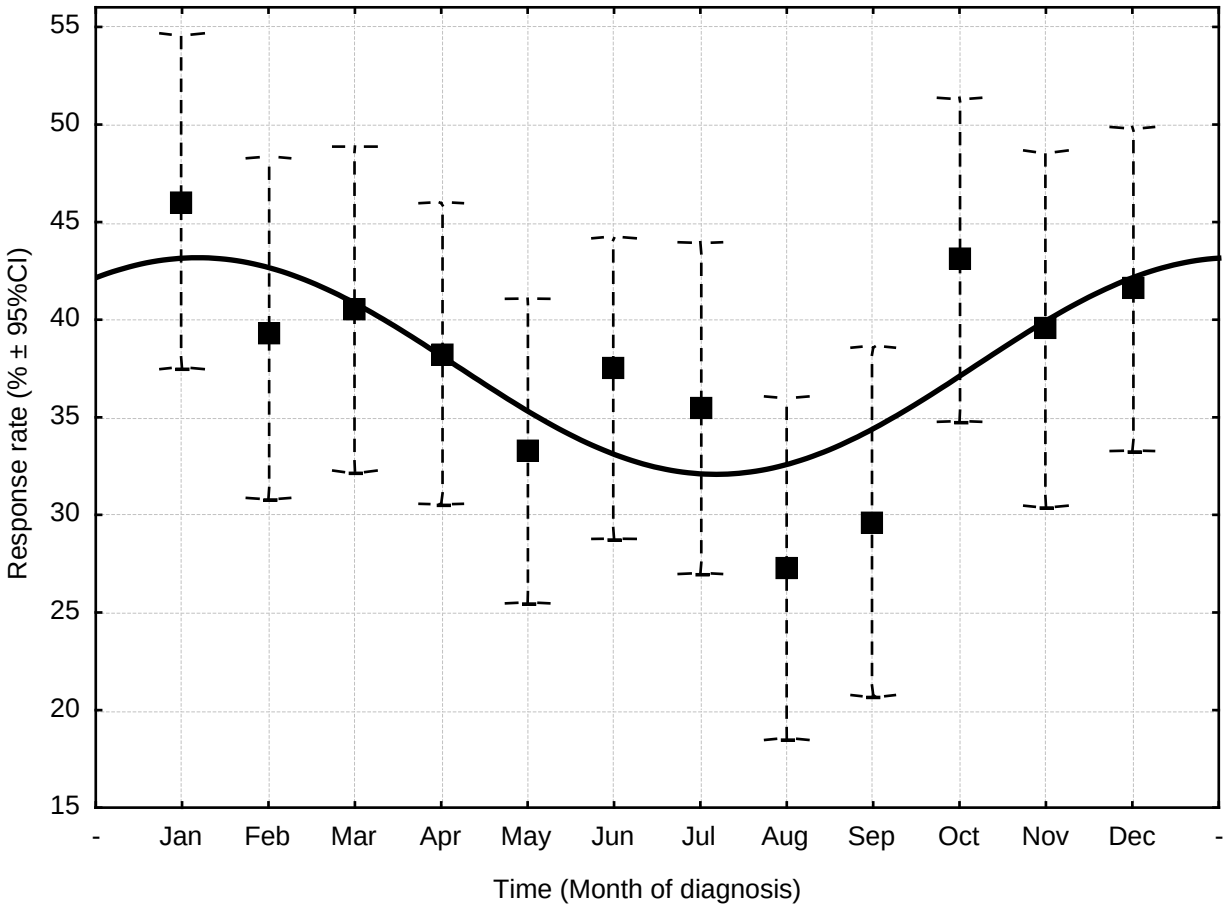
55
50
45
40
35
30
25
20
15
Response rate (% ± 95%CI)
-
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
-
Time (Month of diagnosis)

Figure 2

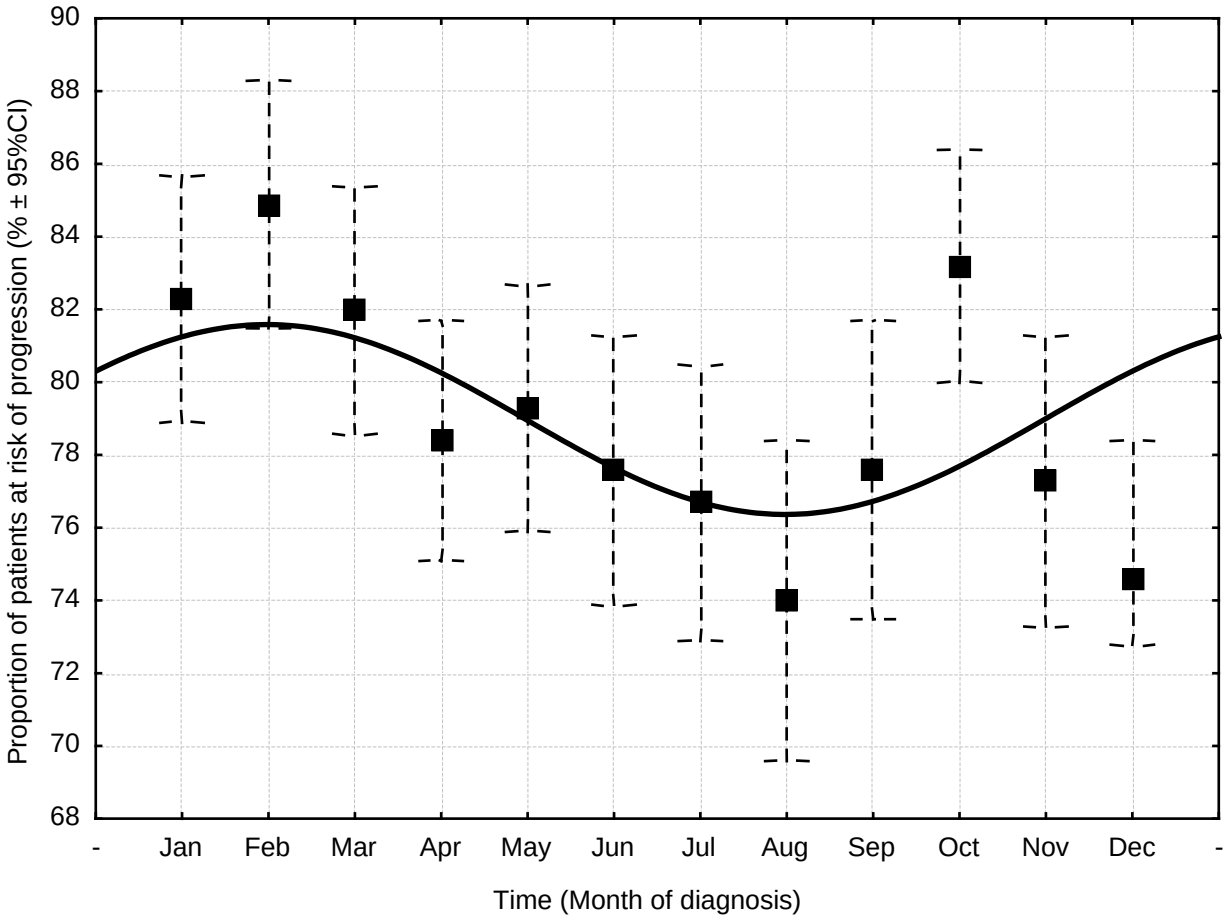
Proportion of patients at risk of progression (% ± 95%CI)
90
88
86
84
82
80
78
76
74
72
70
68
-
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
-
Time (Month of diagnosis)

Figure 3

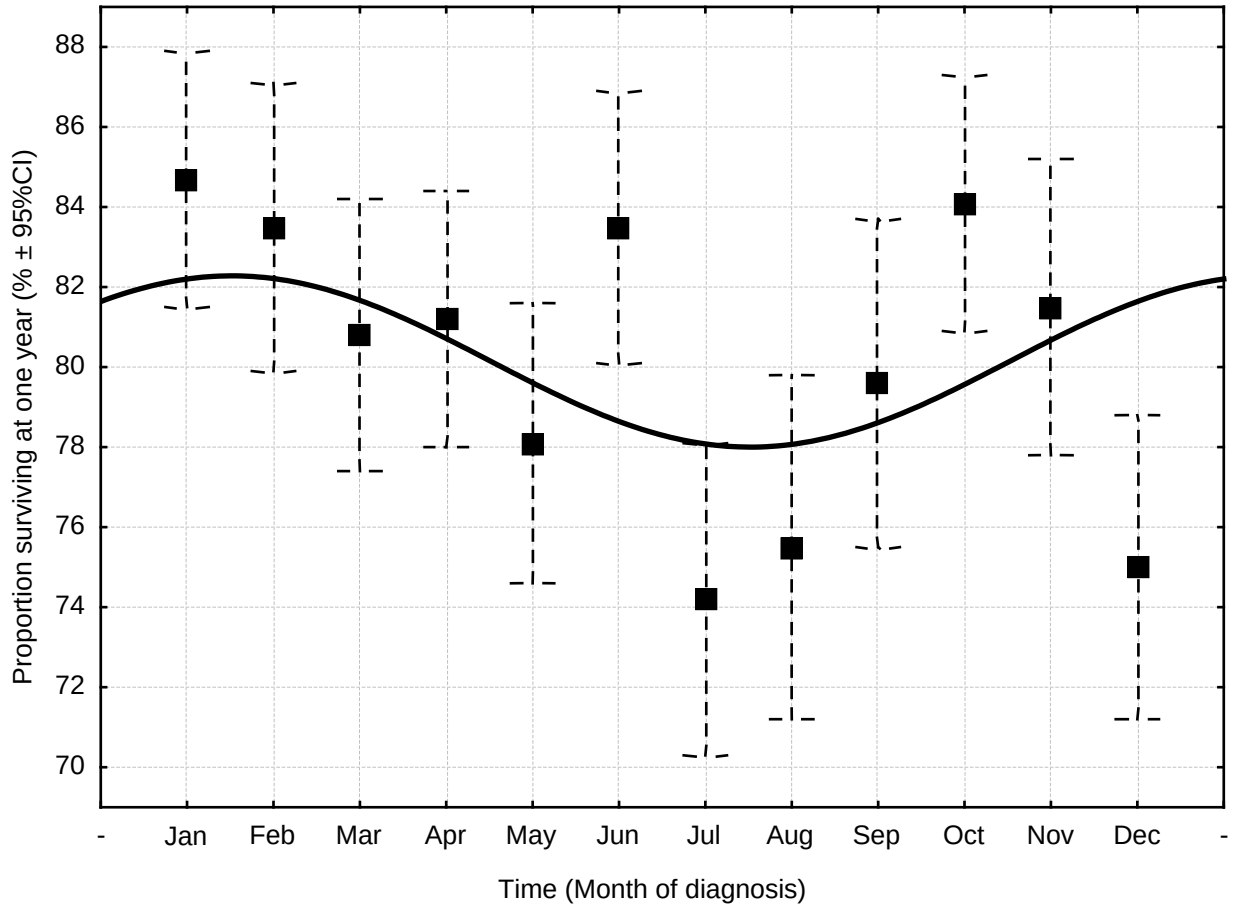
Proportion surviving at one year (% ± 95%CI)
88
86
84
82
80
78
76
74
72
70
-
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
-
Time (Month of diagnosis)

Figure 4