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PRIMITIVE COLORECTAL TUMOURS AND METASTASES: A BRIEF REPORT ON 31 FEMALES WITH STAGE IV DISEASE

Serra N.,[1*] Reginelli A.,[2] Di Grezia G.,[2] Gatta G.,[2]
Raucci A.,[2] Somma F.,[4] Cappabianca S.,[2] Di Carlo P.[3]

[1]*School of Medicine and Surgery, University Federico II of Naples, Italy*

[2]*Department of Radiology and Radiotherapy, University of Campania "Luigi Vanvitelli", Naples, Italy*

[3]*Department of Sciences for Health Promotion and Mother & Child Care, Infectious Diseases Section, University of Palermo, Italy*

[4]*Neuroradiology Centre, PO "Santa Maria di Loreto Mare", ASL NA1, Naples, Italy*

*nicola.serra@unina.it

Abstract

We analysed primary tumour in the colon, with particular attention to the rectum and to metastatic patterns identified by computed tomography, in a female with advanced disease.
This was a retrospective study involving a sample of 91 patients, where only 31 women with stage IV disease according to RECIST criteria and histologically confirmed primary colon cancer (54.84% with only rectum cancer) were considered.
Our study revealed that the most common secondary sites in these patients with primary colon cancer were the lungs (p-value<0.005) and liver (p-value < 0.005). Since the primary colon tumour was located in the rectum more frequently than in other parts of the colon (54.84% = 17/31), an investigation on secondary sites of metastases from CRC (colorectal cancer) was performed. The most common secondary sites of metastases from CRC were the lungs and liver. Univariate analysis showed a significant negative linear correlation between lungs and peritoneum (R = -0.733, p-value = 0.0008) and between lungs and regional lymph nodes (R = -0.708, p-value = 0.0015). On the other hand, there was a significant positive linear correlation between ovaries and small intestine (R = 0.850, p-value < 0.0001), ovaries and adrenal glands (R = 0.928, p-value < 0.0001), regional lymph nodes and peritoneum (R = 0.740, p-value = 0.0007) and between small intestine and adrenal glands (R = 0.758, p-value = 0.0004).
Finally, multivariate analysis showed that the small intestine and adrenal glands were significant positive predictors of metastases to the ovaries compared to others.

Keywords: colorectal cancer, women, stage IV disease, disease management, metastatic sites.

Introduction

Colorectal cancer (CRC) is the third most common cause of cancer death in Western Europe and North America [1,2] and the second most frequently diagnosed cancer, accounting for about 13% of all cancer diagnoses [3].

Over the last few years, clinical outcome for patients with metastatic CRC (mCRC) has improved greatly due to a more strategic approach and to the involvement of a multidisciplinary team to assist in the treatment and management of these patients in a rapidly evolving treatment setting [4].

There is evidence that gender influences the clinical course of colorectal cancer and can also affect disease severity; indeed, women tend to have a more benign course than men. The reasons for this are not completely understood, but likely reflect complex interactions between gender-related differences in exposure to hormones and risk factors [5,6]. Gender differences in risk patterns may also help explain why a larger proportion of tumours in women are located in the proximal colon, specifically 45% versus 36% in men [7].

There were 19,202 deaths (10,406 males and 8796 females) from colorectal cancer in Italy in 2012 [8], and 54% of them were men. The neoplasm ranks second in cancer mortality (10% males and 12% females) and between second and third place in the various stages of life. Fortunately, mortality rate for this disease is declining for both men (-0.6% a year) and, more noticeably, for women (-1.2% a year) [8].

Metastasis to distant organs is responsible for most cancer-related deaths in solid tumours (including CRC) [9,10]. This is due to a lack of effective therapies against disseminated disease. Thus, there is an urgent need to fill this gap in cancer treatment.

It is well known that the most common metastatic sites in CRC patients are the liver and the lungs [11,12]. Periodic colonoscopy, ultrasound (US), and multi detector computed tomography (MDCT) to localize recurrent CRC in the early stages is often performed during follow-up.

Recent studies have analysed the distribution of metastatic site(s) and proposed a metastatic pattern of colon and rectum cancers in CRC patients [12]. Moreover, ovarian metastasis in women with colorectal cancer is under debated. New criteria and diagnostic imaging techniques (US, CT, MRI) are used in the presence of ovarian metastases [12-14].

In recent years, the literature has reviewed therapeutic approaches and prognosis in patients with advanced colorectal cancer, looking at surgical procedures and the operability of cancer lesions and/or the timing of radiochemotherapy for patients with stage IV disease [14]. Health-related quality of life (HRQOL) has become increasingly important in evaluating health services in clinical practice for advanced-stage cancer patients. It is often also linked to fast diagnosis, and to the most appropriate diagnostic tool used to identify the presence of CRC and the most efficient therapy. In this direction, information about the latest developments in the treatment of these tumour types and associated metastases sites is very important [31-36, 38,39,44,61].

In addition to patients undergoing colon or rectum surgery, there are inevitable consequences added to the cancer disease, such as bacteria, fungal and viral infections [39-43,45-49,57,60,64, 65,69,70,71,73]. In particular, a clinical picture characterized by gastrointestinal disorder due to CRC can also be due to viral infections (Norovirus [NV], Rotavirus [RV] and Adenovirus [AV]) that are common in immunocompromised and cancer patients [50-59,62,63,66-68,72].

In line with these studies, we carried out a retrospective analysis of women with advanced CRC to identify new cancer management pathways.

Materials and Methods

Study population and eligibility

From May 2012 to December 2014, we identified 91 patients (49 females and 42 males) with intestinal cancer. Thirty-one of them met our eligibility criteria and were enrolled in the study.

These patients fulfilled the following eligibility requirements:

Inclusion criteria:

I) female, with histologically confirmed stage IV primary intestinal carcinoma, in progression after standard therapy;

II) the patient was ≥ 18 years of age, with a life expectancy of more than 3 months.

Figure 1 shows the study process.

This preliminary study was designed to evaluate the correlation between secondary sites and the most frequent sites of metastases from a primary tumour located in the colon or CRC in patients with advanced intestinal cancer. 31 female patients were enrolled in the study: 17 had rectum cancer (9 in rectum, 4 in recto-sigmoid and six cases where there was multiple primary cancer of the colon, 4 including rectum), confirmed by computed tomography (CT). Baseline patient demographics and disease characteristics were generally well balanced in the treatment group, and all patients had colon adenocarcinoma histologically confirmed.

The Ethics Committee approved our study and all the patients gave informed consent.

Study design

All the patients received at least one cycle of the study medication. The following data were collected and analysed: age at diagnosis, primary tumour site and recurrences, lymph node metastases, CT images of secondary site masses and lymphatic and vascular invasion of secondary sites in order to determine metastatic routes to these organs. All the patients who received chemotherapy had measurable disease on CT scan, and response was evaluated every 2 or 3 months according to RECIST criteria □15□. Secondary sites of metastasis from CRC were compared and analysed.

CT protocol

Computer Tomography examinations were performed with a multi-slice scanner (Toshiba Aquilon), taking a whole-body scan for each patient. The images were acquired without or 70 s after the injection of an iodinated contrast agent. CT raw data of the brain, neck, thorax and abdomen were acquired with 2,5 mm and 1,5 mm slices and reconstructed.

Statistical analysis

Statistical analyses were performed using Matlab statistic toolbox ver. 2008 for Windows at 32 bit.

Data were presented as number and percentage for categorical variables, and continuous data were expressed as mean ± SD, unless otherwise specified. The chi-square test and Yates's continuity correction or Fisher's exact test were used to compare the differences between two percentages or proportions, and we used the multiple comparison chi-square test to define significant differences among percentages, and residual analysis with the Z-test to locate the highest or lowest percentages of secondary location presence for unpaired data.

Instead for paired data, the multiple comparison Cochran's Q test was used to compare the differences among more percentages or proportions under null hypothesis that there are no differences between the variables. When the Cochran's Q test was positive (p-value less than 0.05) then a minimum required difference for a significant difference between two proportions was calculated with Sheskin's test (Sheskin. 2004). The Cochran's Q test and Sheskin's test were performed because we considered cases where there were more secondary locations identified by primary location, which were described individually.

Multi-comparison tests on continuous data were performed with the one-way ANOVA test to evaluate significant differences among means: if the ANOVA test was positive, Scheffè test was performed for pairwise comparison. Univariate and multivariate linear correlation analyses were performed. Tests on Pearson's linear correlation coefficient R were performed with t-Student test, under null hypothesis of Pearson's linear correlation coefficient R = 0. To perform linear correlation analysis on secondary sites of metastases, we defined an experimental probability distribution [37] of secondary sites: *lungs, liver, small intestine, regional lymph nodes, ovary, peritoneum, uterus, pancreas,* and *adrenal glands*, assigning a score of 1 when metastases

were present and 0 when metastases were absent. Finally all tests with p-value < 0.05 were considered significant.

Results

The 31 females with stage IV disease, with ages in the range 34-85, mean 62.19 y.o. and standard deviation (*SD*) 10.92 y.o., were diagnosed at initial presentation with a primary tumour in: the ascending colon (16.13% - 5/31), descending colon (9.68% - 3/31), rectum colon (29.03% - 9/31), sigmoid colon (12.90% - 4/31), recto-sigmoid colon (12.90% - 4/31) and with multiple primary carcinoma of the colon (19.35% - 6/31). A total of 54.84% (17/31) had rectum cancer. This subgroup were in the age range 34-80, mean 62.12 y.o. and standard deviation (*SD*) 11.84 y.o.. All of them met the study's inclusion criteria and were enrolled.

Table 1 reports primary colon cancer and secondary metastatic location.

A multi-comparison test (Table 2) showed that there were no significant differences among the presence of primary tumours detected in this study (p-value = 0.380).

Instead, there were significant differences among secondary locations (p-value < 0.001). The most common were: lungs (p-value < 0.005) and liver (p-value < 0.005), while adrenal glands (p-value < 0.005), pancreas (p-value < 0.005), uterus (p-value < 0.005) and small intestine (p-value < 0.005) were less common (Table 2).

Subsequently, we focused our attention on the rectum. We observed rectum involvement in 17 of the 31 females in the study (54.84%). Table 3 shows the characteristics of this subgroup. Multi-comparison testing revealed significant differences among secondary sites from CRC (p-value < 0.001). In particular:

- the most common secondary locations were the lungs (p-value < 0.05) and the liver (p-value < 0.05);
- the least common secondary locations were the adrenal glands (p-value < 0.05) and small intestine (p-value < 0.05).

In Table 4, we analysed the univariate and multivariate linear correlation among secondary locations for the 17 patients with primary involvement of the rectum. In addition, univariate analysis showed a significant negative linear correlation between lungs and peritoneum (R = -0.733, p-value = 0.0008), and between lungs and regional lymph nodes (R = -0.708, p-value = 0.0015). On the other hand, there was a significant positive linear correlation between ovaries and small intestine (R = 0.850, p-value < 0.0001), ovaries and adrenal glands (R = 0.928, p-value < 0.0001), regional lymph nodes and peritoneum (R = 0.740, p-value = 0.0007) and between small intestine and adrenal glands (R = 0.758, p-value = 0.0004). Multivariate analysis showed that small intestine and adrenal glands were significant positive predictors of metastases to the ovaries compared to others. Finally, there was no correlation between age and site of metastases.

Discussion

In our study, primary CRC was mainly located in the distal part of the colon and/or rectum. This is probably due to the fact that our women were on average older than those in other epidemiological studies that included women with personal or family risk of polyposis [16].

We conducted an investigation of primary sites and metastases, finding statistical significance only for the sites described as the most common sites of metastasis in patients with CRC, namely the liver and the lungs.

Analysing the scientific literature, we observed that a lot of research studies focus on single metastatic sites without considering other sites that are subsequently involved or turn out to be involved during follow up, especially in advanced-stage disease [17].

This could represent a limitation in the investigation of secondary sites. In fact, a review of autopsy data from patients who died from colorectal cancer showed that the liver is the only site of metastatic disease in one third of patients [19].

Especially now, in the light of new lung cancer treatments and new hepatic surgical strategies, studies like this one that examine the correlation between different metastatic sites may be useful

for improving the survival rate of patients in both advanced and earlier stages of disease, and could contribute to the evaluation of cost-benefit ratio [20].

The prognosis of rectal cancer and colon cancer is different, and the comparative study of different metastatic sites could be important. Cancer location may be used as a reference for personalized adjuvant therapy and postoperative follow-up surveillance programs. Lower threshold for adjuvant therapy in rectal and left-sided colon cancers, and more aggressive surveillance of lung metastasis by chest X-ray or CT should be considered [18-21].

Studies involving a large number of subjects have examined the influence of gender on prognosis and suggested that gender may in fact have an impact [24]. For this reason, the authors selected and studied a population of women with advanced CRC, because hormones have a more favourable effect, in younger women particularly.

Although our subjects with rectum cancer were on average older than those in other European epidemiological reports, the involvement of the rectum, either as a single lesion alone or with colon involvement, opens up the debate on the surgical and radiotherapy management of advanced stage colorectal cancer in women with pelvic involvement [27,28].

Finally, our study analysed metastatic spread pattern in 31 advanced-stage female patients whose follow-up care included CT scans. CT remains the "workhorse" of follow-up imaging for the routine surveillance of colorectal cancer in this class of patients. Recent studies have shown that clinicians could also consider magnetic resonance when choosing which type of imaging to use; although more expensive for the patient, this technique is better for determining pelvic recurrence of rectal cancer [28,29]. Albeit our study was conducted on a small number of subjects, all the patients were investigated for pathological factors including primary tumour characteristics, which is a warranty for the results obtained and an encouragement to conduct further investigations on therapeutic decisions in colorectal cancer.

Colorectal cancer is an active area of scientific research therefore our data could be used to manage advanced stage CRC where the clinical oncologist has to envisage not only a combined treatment approach but also a multistep approach regarding the primary site [14,29,30].

Finally, we suggest that investigations on large patient samples from different geographical areas are carried out, and that these studies include only patients with advanced CRC tumour, subdividing them by primary sites of the colon and rectum.

Competing interests

The authors declare that they have no competing interests.

Approval

All authors read and approved the final manuscript.

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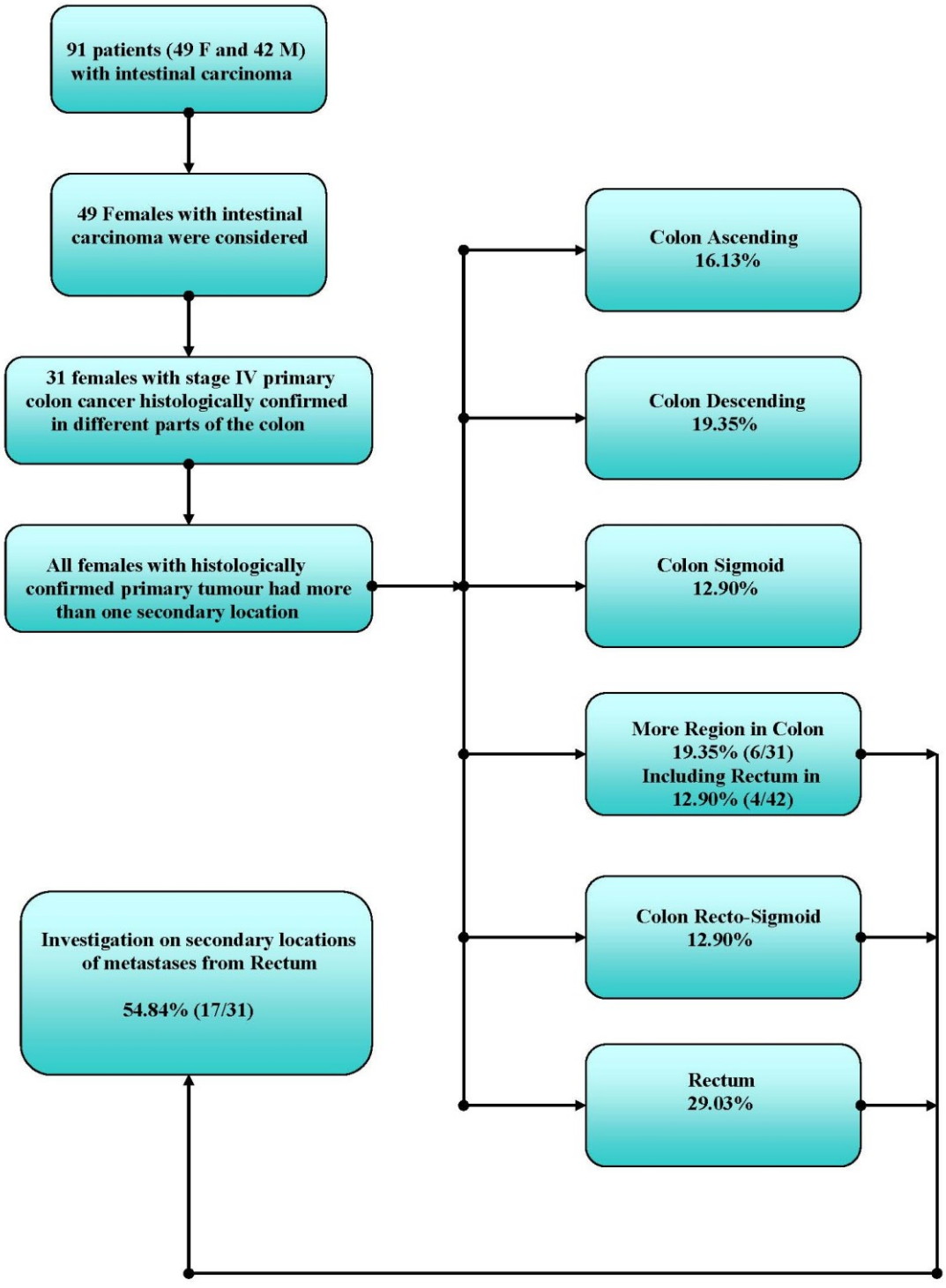

73.

Figure 1. Flow chart of our study
(more than one region in colon)

Table 1. Percentage of patients with primary tumour and primitive locations with metastases following clinical examination with CT

	Primary cancer in colon						
	MPCC	**Ascending**	**Descending**	**Rectum**	**Sigmoid**	**Recto-sigmoid**	
	19.35 (6/31)	16.13 (5/31)	9.68 (3/31)	29.03 (9/31)	12.90 (4/31)	12.90 (4/31)	
	Secondary Locations						**Total %**
Lungs	16.13 (5/31)	6.45 (2/31)	6.45 (2/31)	22.58 (7/31)	9.68 (3/31)	12.90 (4/31)	74.19 (23/31)
Liver	3.23 (1/31)	6.45 (2/31)	3.23 (1/31)	22.58 (7/31)	9.68 (3/31)	12.90 (4/31)	59.06 (18/31)
Regional Lymph Nodes	3.23 (1/31)	3.23 (1/31)	3.23 (1/31)	12.90 (4/31)	6.45 (2/31)	3.23 (1/31)	32.26 (10/31)
Ovaries	3.23 (1/31)	6.45 (2/31)	0.00	9.68 (3/31)	3.23 (1/31)	0.00	22.59 (7/31)
Peritoneum	6.45 (2/31)	3.23 (1/31)	0.00	3.23 (1/31)	3.23 (1/31)	3.23 (1/31)	19.35 (6/31)
Small intestine	3.23 (1/31)	3.23 (1/31)	0.00	3.23 (1/31)	3.23 (1/31)	0.00	12.90 (4/31)
Adrenal glands	0.00	0.00	0.00	3.23 (1/31)	3.23 (1/31)	0.00	6.45 (2/31)
Pancreas	0.00	0.00	0.00	0.00	3.23 (1/31)	0.00	3.23 (1/31)
Uterus	0.00	0.00	0.00	0.00	3.23 (1/31)	0.00	3.23 (1/31)

MPCC = multiple primary cancer of the colon

Table 2. Multi-comparison test among primary tumour locations and among all secondary sites of metastasis in reference to clinical examination with CT

Locations	Multivariate p-value	Highest / Lowest frequency (Locations)	Localized p-value
Primary location	0.380 (C)	–	–
Ascending			
Descending			
Rectum			
Sigmoid			
Recto-sigmoid			
MPCC			
Secondary location	< 0.001* (Q)		
Lungs		Lungs **	< 0.005* (S)
Liver		Liver **	< 0.005* (S)
Regional lymph nodes			
Ovaries			
Small intestine		Adrenal glands ***	< 0.005* (S)
Peritoneum		Pancreas ***	< 0.005* (S)
Adrenal glands		Uterus ***	< 0.005* (S)
Pancreas		Small intestine ***	< 0.005* (S)
Uterus			

* = Significant test; ** = most frequent; *** = less frequent; MPCC = multiple primary cancer of the colon; Z = Z test; C = multicomparison chi-square test; Q = multicomparison Cochran's Q test; S = Sheskin's test

Table 3. Percentage of patients with CRC and secondary locations with metastases following clinical examination with CT. A multiple comparison test among secondary sites from CRC was performed

Secondary sites from CRC	Percentages	Multivariate p-value	Highest/lowest frequency (Locations)	Localized p-value
Lungs	82.35% (14/17)	< 0.001* (Q)	Lungs **	< 0.05* (S)
Liver	64.71% (11/17)		Liver **	< 0.05* (S)
Regional lymph nodes	16.13% (5/17)			
Ovaries	23.53% (4/17)			
Peritoneum	23.53% (4/17)			
Small intestine	5.88% (1/17)		Small intestine ***	< 0.05* (S)
Adrenal glands	5.88% (1/17)		Adrenal glands***	< 0.05* (S)

* = Significant test; ** = most frequent; *** = less frequent; Q = multicomparison Cochran's Q test; S = Sheskin's test

Table 4. Univariate and multivariate linear correlation analysis among secondary sites from primary CRC

Correlation among sites of metastasis	Univariate analysis	Multivariate analysis
	R (p-value)	Multiple linear correlation coefficient: 0.842
Lungs / Liver	0.411 (0.102)	*R_partial*: 0.256 p-value = 0.421
Lungs / Regional lymph nodes	-0.708 (0.0015) *	*R_partial*: 0.145 p-value = 0.217
Lungs / Ovaries	-0.408 (0.105)	*R_partial*: -0.030 p-value = 0.927
Lungs / Peritoneum	-0.733 (0.0008) *	*R_partial*: -0.360 p-value = 0.250
Lungs / Small intestine	-0.444 (0.074)	*R_partial*: -0.330 p-value = 0.295
Lungs / Adrenal glands	-0.329 (0.197)	*R_partial*: 0.141 p-value = 0.662
		Multiple linear correlation coefficient: 0.515
Liver / Lungs	0.411 (0.102)	*R_partial*: 0.256 p-value = 0.421
Liver / Regional lymph nodes	-0.283 (0.272)	*R_partial*: 0.144 p-value = 0.654
Liver / Ovaries	0.0147 (0.956)	*R_partial*: -0.037 p-value = 0.908
Liver / Peritoneum	-0.444 (0.0745)	*R_partial*: -0.228 p-value = 0.476
Liver / Small intestine	0.0275 (0.917)	*R_partial*: 0.150 p-value = 0.642
Liver / Adrenal glands	0.033 (0.900)	*R_partial*: 0.015 p-value = 0.963
		Multiple linear correlation coefficient: 0.964
Ovaries / Lungs	-0.408 (0.105)	*R_partial*: -0.030 p-value = 0.927
Ovaries / Regional lymph nodes	0.353 (0.165)	*R_partial*: 0.124 p-value = 0.702
Ovaries / Liver	0.0147 (0.956)	*R_partial*: -0.037 p-value = 0.908
Ovaries / Peritoneum	0.193 (0.458)	*R_partial*: -0.085 p-value = 0.793
Ovaries / Small intestine	0.870 (<0.0001) *	*R_partial*: 0.646 p-value = 0.0232 *
Ovaries / Adrenal glands	0.928 (<0.0001) *	*R_partial*: 0.811 p-value = 0.0014 *
		Multiple linear correlation coefficient: 0.822
Regional lymph nodes / Lungs	-0.708 (0.0015) *	*R_partial*: -0.385 p-value = 0.217
Regional lymph nodes / Liver	-0.283 (0.272)	*R_partial*: 0.144 p-value = 0.654
Regional lymph nodes / Ovaries	0.353 (0.165)	*R_partial*: 0.124 p-value = 0.702
Regional lymph nodes / Peritoneum	0.740 (0.0007) *	*R_partial*: 0.476 p-value = 0.118
Regional lymph nodes / Small intestine	0.243 (0.348)	*R_partial*: -0.311 p-value = 0.326
Regional lymph nodes / Adrenal glands	0.351 (0.167)	*R_partial*: 0.121 p-value = 0.707
		Multiple linear correlation coefficient: 0.822
Peritoneum / Lungs	-0.733 (0.0008) *	*R_partial*: -0.360 p-value = 0.250
Peritoneum / Liver	-0.444 (0.0745)	*R_partial*: -0.228 p-value = 0.476
Peritoneum / Ovaries	0.193 (0.458)	*R_partial*: -0.085 p-value = 0.793
Peritoneum / Regional lymph nodes	0.740 (0.0007) *	*R_partial*: 0.476 p-value = 0.118
Peritoneum / Small intestine	0.182 (0.484)	*R_partial*: 0.042 p-value = 0.897
Peritoneum / Adrenal glands	0.167 (0.521)	*R_partial*: 0.004 p-value = 0.989

		Multiple linear correlation coefficient: 0.900
Small intestine / Lungs	-0.444 (0.074)	*R_partial*: -0.330 p-value = 0.295
Small intestine / Liver	0.0275 (0.917)	*R_partial*: 0.150 p-value = 0.642
Small intestine / Ovaries	0.870 (<0.0001) *	*R_partial*: 0.646 p-value = 0.0232 *
Small intestine / Regional lymph nodes	0.243 (0.348)	*R_partial*: -0.311 p-value = 0.326
Small intestine / Peritoneum	0.182 (0.484)	*R_partial*: 0.042 p-value = 0.897
Small intestine / Adrenal glands	0.758 (0.0004) *	*R_partial*: -0.192 p-value = 0.549
		Multiple linear correlation coefficient: 0.936
Adrenal glands / Lungs	-0.329 (0.197)	*R_partial*: 0.141 p-value = 0.662
Adrenal glands / Liver	0.033 (0.900)	*R_partial*: 0.015 p-value = 0.963
Adrenal glands / Ovaries	0.928 (<0.0001) *	*R_partial*: 0.811 p-value = 0.0014 *
Small intestine / Regional lymph nodes	0.351 (0.167)	*R_partial*: 0.121 p-value = 0.707
Adrenal glands / Peritoneum	0.167 (0.521)	*R_partial*: 0.004 p-value = 0.989
Adrenal glands / Small intestine	0.758 (0.0004) *	*R_partial*: -0.192 p-value = 0.549
		Multiple linear correlation coefficient: 0.761
Age / Lungs	0.289 (0.260)	*R_partial*: -0.134 p-value = 0.694
Age / Liver	-0.288 (0.263)	*R_partial*: -0.508 p-value = 0.111
Age / Regional lymph nodes	-0.385 (0.128)	*R_partial*: 0.381 p-value = 0.248
Age / Ovaries	-0.384 (0.128)	*R_partial*: -0.233 p-value = 0.490
Age / Peritoneum	-0.338 (0.185)	*R_partial*: -0.329 p-value = 0.323
Age / Small intestine	-0.478 (0.052)	*R_partial*: -0.476 p-value = 0.139
Age / Adrenal glands	-0.420 (0.093)	*R_partial*: -0.319 p-value = 0.339

R = Pearson's linear correlation coefficient; * = significant test; R_partial = the partial correlation coefficient is the coefficient of correlation of the variable with the dependent variable, adjusted for the effect of the other variables in the model

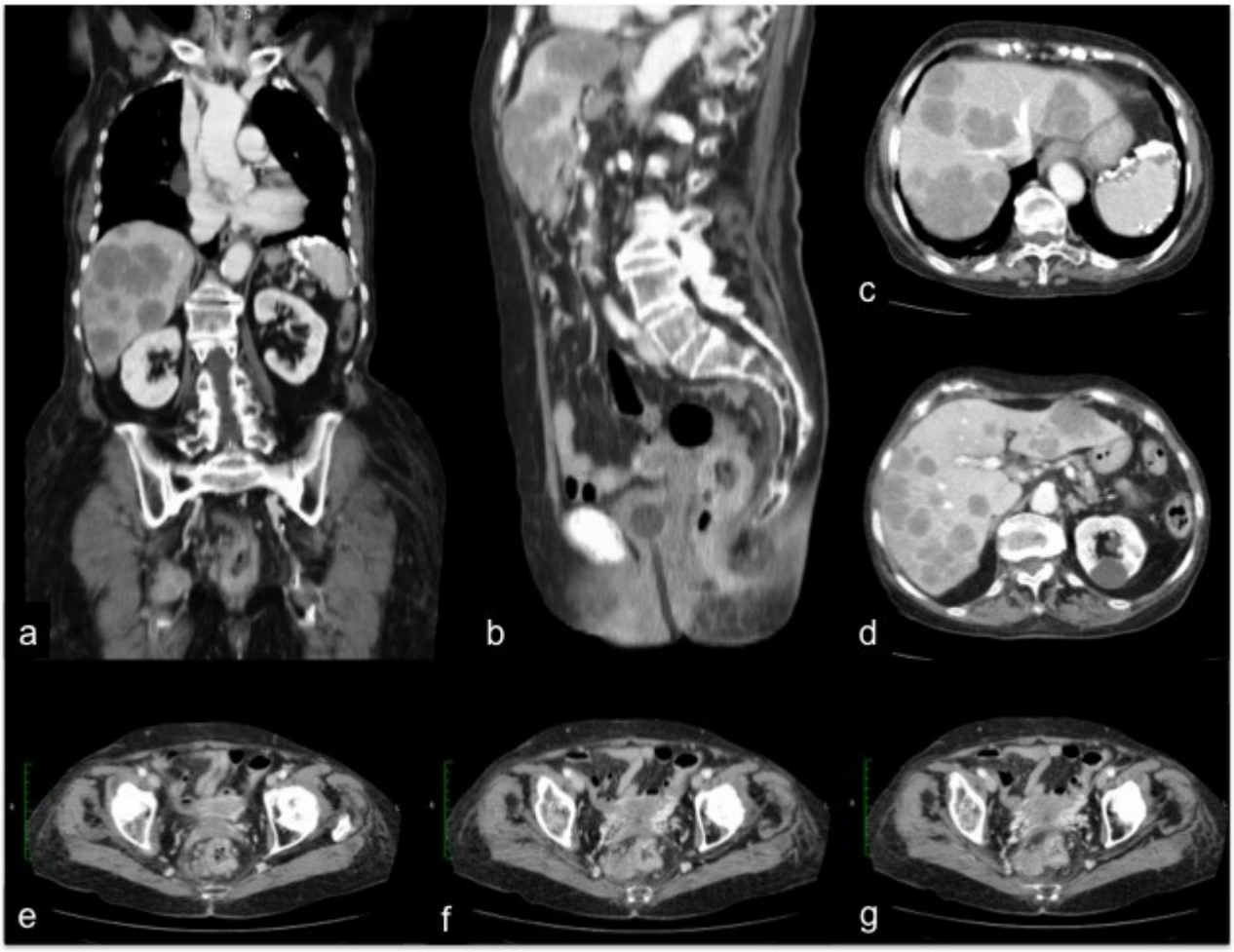

Figure 2. Coronal (a*)* and Sagittal (b) reconstruction of a contrast-enhanced MDCT of 85 y.o. female patient in advanced stage of rectal cancer.

Axial images show multiple metastatic hepatic nodules ranging from 8 to 90 mm in diameter, localized in all hepatic segments (c, d); (e, f, g) show an irregular thickening of the rectal wall that involves the perirectal fat and extends through the mesorectal fascia; non cleavage plan. Intra and extramesorectal lymph nodes are involved.