Colorectal Cancer Metastases In The Reproductive Tract – A Systematic Review

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Abstract

BACKGROUND: Colorectal cancer metastases are common and usually affect the liver, lungs, peritoneum or bone. However, unusual cases of metastatic disease within the reproductive tracts of both male and female patients have been described. This review aims to collate and summarise the available data to aid clinical decision making and patient counselling.

METHODS: Pubmed, MEDLINE and the Cochrane databases were searched from inception till November 2020 for case reports and cases series describing original data on colorectal cancer metastases within the reproductive tract.

RESULTS: 29,216 results were filtered down to 89 studies for inclusion. 43 and 46 related to the male and female reproductive tracts respectively, with individual patient outcomes reported for 48 males and 461 females. Genital metastases were associated more with rectal cancers whilst ovarian and testicular tumours more commonly derived from colonic primaries. Treatment was with curative intent for the minority of male patients (32%) with an associated poor prognosis (4% 5-year overall survival). Female reproductive tract metastases with ovarian lesions in particular were more likely to receive curative intent treatment (63%) and superior long-term survival (17% 5-year overall survival)

CONCLUSIONS: Reproductive system colorectal cancer metastases are rare with limited cases reported. They are associated with advanced primary tumours and disseminated disease with an associated poor prognosis.

1. Introduction

Globally, colorectal cancer (CRC) is the third most common cancer for both men and women and the second most common cause of cancer-related death¹. 20% of patient have metastases on diagnosis² with a further 20% of patients developing metachronous disease after initial surgery³. The most commonly affected sites are the liver (70%), thorax (32%), peritoneum (21%) and bone (12%)⁴. Despite progress in the treatment of metastatic CRC, prognosis remains poor. Relative 5-year survival rates with Stage IV disease are at most 12%⁵.

Treatment of metastatic disease is increasingly routine and effective. Surgical resection of solitary liver or lung metastases can lead to 5-year survival rates of 40%⁶ and 50%⁷, respectively. However, metastatic disease at unusual sites is more poorly understood. There are published cases of cutaneous^{8,9}, central-nervous system^{10,11}, gastro-intestinal^{12,13}, urinary system^{14,15} and skeletal muscle¹⁶ metastases amongst others. Although a rare occurrence, the high prevalence of CRC and increasing survival amongst patients with advanced disease means it is not uncommon for the average colorectal cancer centre to see unusual patterns of disease. When this occurs, an understanding of the likely progression of the disease and the optimal treatment is vital for clinical decision making and patient counselling.

One potential site for metastases is the reproductive tract of both males and females. Ovarian metastases (OM) or 'Krukenberg' tumours are the most common of these with reported prevalence rates of 3-5% amongst patients with CRC¹⁷. These patients however, retain a poor prognosis in comparison to liver or lung metastases with a 5-year survival rate of 12%¹⁷. In addition to this, genital, cervical, uterine or scrotal metastases have all been described. The rarity of these cases means prognosis and optimal treatment for these patients is very poorly understood amongst clinicians.

Data on reproductive tract CRC metastases are largely confined to individual case reports or within small case series. This review aims to collate and summarise these cases in order to aid clinician and patient understanding of these rare cases.

2. Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹⁸.

2.1 Search strategy

A systematic search was performed using Pubmed, MEDLINE and the Cochrane Library databases, from inception till September 2020. Results were filtered to include human studies only.

The following search algorithm was used:

(Colorectal cancer metastasis OR rectal cancer metastasis OR colon cancer metastasis) AND (rare OR unusual OR atypical OR non-typical OR uncommon OR abnormal OR irregular OR isolated OR peculiar).

2.2 Eligibility criteria

Inclusion:

All case series or case reports reporting original data on colorectal metastases in the male or female reproductive system

Studies published on any date

Exclusion:

Non-English language studies

Non-human subject studies

2.3 Study selection

One author (JA) manually screened each article identified by the initial search, using the study title and abstract in reference to the eligibility criteria. Screened articles were then included in a full text review to

confirm final eligibility. Full-text review and data extraction was completed independently by five authors using a standardised tailored form.

2.4 Data extraction and synthesis

The following data was extracted from all included papers: site of primary tumour, site of metastasis, age, sex, ethnicity, significant past medical history, histology of primary tumour, initial staging, treatment of primary tumour, synchronous vs metachronous tumours, time interval from primary tumour and metastasis, mode of presentation, histology of metastasis, treatment of metastasis, length of follow-up, death due to disease progression.

Pooled rates have been calculated for outcomes with common denominators.

3. Results

3.1 Selected studies

A total of 29,216 records were identified from the initial database searches. Initial screening excluded 29,092 irrelevant records. 7 non-English language records and 20 abstract only records were excluded. 8 studies did not meet the eligibility criteria on full text review leaving a total of 87 studies eligible for inclusion in this study. 42 relate to the female genital tract¹⁹⁻⁶², 44 relate to the male genital tract⁶³⁻¹⁰⁶ and one study reports on both⁵¹.

3.2 Study characteristics

71 studies are case reports and 16 are case series. There is a broad publication date range from 1950-2020. The characteristics of studies involving the male and female reproductive systems are summarised Table 1 and Table 2 respectively. The total number of individual patient data reports are 47 and 461, respectively.

Table 1
– Study characteristics of male reproductive system CRC metastases

Author	Year published	Study design	Site affected	Number of patients included
Male genital tract				
Yang ¹⁰⁶	2020	Case report	Scrotum	1
Wald ¹⁰⁵	2020	Case report	Spermatic cord	1
Smit ¹⁰³	2019	Case report	Testis	1
Singh ⁹⁹	2018	Case report	Testis	1
Kuliavas ⁷⁵	2018	Case report	Penis	1
Kozan ⁷⁴	2016	Case report	Penis	1
Jang ⁹¹	2015	Case report	Spermatic cord	1
Dong ⁷⁰	2015	Case report	Penis	1
Cholin ⁶⁸	2015	Case report	Penis	1
Verma ¹⁰⁴	2013	Case report	Testis	1
Persec ⁸²	2013	Case report	Penis	1
Ozgen ⁹⁷	2013	Case report	Scrotum	1
McGuinness ⁷⁸	2013	Case report	Penis	1
Rampa ¹⁰⁰	2012	Case report	Testis	1
Youssef ⁸⁸	2011	Case report	Prostate	1
Goris Gbenou ⁷¹	2011	Case report	Penis	1
Lee ⁷⁷	2011	Case report	Penis	1
Yildirim ⁸⁶	2010	Case report	Penis	1
Park ⁸¹	2009	Case report	Penis	1
McWeeney ⁹³	2009	Case report	Scrotum	1
Galanis ⁸⁹	2009	Case report	Spermatic cord	1
Gazoni ⁵¹	2008	Case series	Scrotum	3

Author	Year published	Study design	Site affected	Number of patients included
Reuter ¹⁰¹	2007	Case report	Scrotum	1
Ouellette ⁹⁶	2007	Case report	Testis	1
Murhekar ⁸⁰	2007	Case report	Penis	1
Ketata ⁷²	2007	Case report	Penis	1
Chung ⁶⁹	2007	Case report	Penis	1
Appu ⁶³	2006	Case report	Penis	1
Cathomas ⁶⁶	2006	Case report	Penis	1
Anton ⁹⁵	2005	Case report	Spermatic cord	1
Yilmaz ⁸⁷	2004	Case report	Penis	1
Salesi ¹⁰²	2004	Case report	Testis	1
Pesl ⁸³	2004	Case report	Prostate	1
Hyashi ⁹⁰	2003	Case report	Scrotum	1
Tan ⁸⁵	2002	Case report	Penis	1
Polychronidis ⁹⁸	2002	Case report	Spermatic cord	1
Melis ⁹⁴	2002	Case report	Scrotum	1
Banerjee ⁶⁴	2002	Case report	Penis	1
Kanno ⁹²	1994	Case report	Spermatic cord	1
Berman ⁶⁵	1993	Case report	Prostate	1
Mukamel ⁷⁹	1987	Case series	Penis	1
Khubchandani ⁷³	1986	Case report	Penis	1
Kumar ⁷⁶	1980	Case series	Penis	1
Tagart ⁸⁴	1966	Case report	Penis	1
Cattell ⁶⁷	1950	Case report	Penis	1
Total				47

Table 2
– Study characteristics of female reproductive system CRC metastases

Author	Year published	Study design	Site affected	Number of patients included
Female genital tract				
Almas ¹⁹	2020	Case report	Ovary	1
Kornfeld ³⁶	2020	Case report	Cervix	1
Kwon ⁵²	2020	Case report	Vagina	1
Zhu ⁶²	2020	Case report	Vagina	1
Paramythiotis ⁴¹	2019	Case report	Ovary	1
Elumalai ⁴⁹	2019	Case report	Vulva	1
Balaya ²¹	2018	Case report	Fallopian tube	1
Tang ⁶¹	2018	Case report	Vulva	1
Kammar ³⁴	2017	Case series	Ovary	25
Zogbi ⁴⁶	2017	Case report	Ovary	1
Amin ²⁰	2016	Case report	Ovary	1
Kyo ³⁷	2016	Case report	Ovary	1
Shimazaki ⁴³	2016	Case series	Ovary	2
Tajima ⁴⁴	2016	Case report	Ovary	1
Challa ²⁴	2015	Case series	Ovary	7
Ren ⁵⁶	2015	Case report	Vulva	1
Sadatomo ⁵⁸	2015	Case report	Vagina	1
Berhili ²²	2014	Case report	Cervix	1
Akpak ⁴⁷	2014	Case report	Vulva	1
D'Arco ⁴⁸	2014	Case report	Vagina	1
Garrett ³¹	2012	Case series	Ovary	110
Pabuccu ⁵⁵	2012	Case report	Vulva	1

Author	Year published	Study design	Site affected	Number of patients included
Tanaka ⁶⁰	2012	Case report	Vagina	1
Chereux ²⁵	2011	Case report	Cervix	1
Ojo ⁴⁰	2011	Case series	Ovary	26
Sabbagh ⁵⁷	2011	Case report	Vagina	1
Colling ²⁷	2010	Case report	Uterus	1
Fujiwara ³⁰	2010	Case series	Ovary	22
Segelman ⁴²	2010	Case series	Ovary	64
Tan ⁴⁵	2010	Case series	Ovary	25
Funada ⁵⁰	2010	Case report	Vagina	1
Chung ²⁶	2009	Case series	Ovary	34
Kim ³⁵	2009	Case series	Ovary	103
Gazoni ⁵¹	2008	Case series	Vulva	1
Erroi ²⁸	2007	Case series	Ovary	10
Gurbuz ³²	2006	Case report	Ovary	1
Marchal ⁵⁴	2006	Case report	Vagina	1
Tan ⁵⁹	2006	Case series	Vulva	1
Millaire ³⁸	2005	Case report	Cervix	1
Feldman ²⁹	2004	Case report	Ovary	1
Ohsawa ³⁹	2003	Case report	Ovary	1
Birnkrant ²³	1986	Case report	Ovary	1
Lee ⁵³	1974	Case series	Vagina	2
			Total	461

3.3 Presentation

The mode of presentation was not reported for 407/509 (80%) patients. In studies which did report this it was possible to describe the mode of presentation as either 'symptomatic', 'incidental' or from a formal 'surveillance' programme. A summary of presentation mode is found in Table 3.

For females, the majority (92%) of ovarian lesions do not have mode of presentation specified. However, in vulvar, cervical, salpingeal and uterine metastases, there was a trend towards a symptomatic presentation. Vaginal metastases presented with vaginal bleeding or pelvic pain, vulvar metastases as palpable superficial lesions or with bleeding/discharge. Symptomatic uterine and cervical metastases all presented with vaginal bleeding. The one patient with salpingeal metastases presented with watery vaginal discharge.

Reporting was more complete for males and again demonstrated a trend towards symptomatic presentations. Penile metastases presented as painless or painful superficial lesions and scrotal secondaries displayed ulcerating skin lesions. Testicular and spermatic cord metastases tended to be painful with associated palpable masses.

Table 3
– Summary of presentation with reproductive tract CRC metastases

		Not specified (%)	Surveillance (%)	Symptomatic (%)	Incidental (%)	Totals
Female	Ovary	405 (92)	21 (5)	10 (2)	2 (<1)	438
	Vagina	1 (10)	0	7 (70)	2 (20)	10
	Vulva	2	1 (14)	4 (57)	0	7
	Cervix	0	0	4 (100)	0	4
	Fallopian tube	0	0	1 (100)	0	1
	Uterus	0	0	1 (100)	0	1
Male	Penis	6 (29)	1 (4)	16 (67)	0	23
	Scrotum	4 (44)	1 (11)	4 (44)	0	9
	Testis	0	0	5 (83)	1 (17)	6
	Spermatic cord	0	0	6 (100)	0	6
	Prostate	1 (33)	0	2 (67)	0	3

All studies report the presentation of metastases as either synchronous or metachronous. Synchronous is used to describe metastases which are diagnosed at the same time as (or in some papers within 6 months of) the diagnosis of the original tumour. Metachronous is used to describe recurrence of previously treated disease.

Mode of presentation was reported on for >99% (504/508) of included patients. Table 4 summarises this outcome for each site of metastasis and demonstrates a largely comparable distribution between synchronous or metachronous presentations.

Table 4
– Summary of synchronous vs metachronous presentations of metastases

		Not Specified (%)	Synchronous (%)	Metachronous (%)
Female	Ovary	0	299 (68)	139 (32)
	Vagina	0	7 (70)	3 (30)
	Vulva	1 (14)	1 (14)	5 (71)
	Cervix	0	0	4 (100)
	Fallopian tube	0	0	1 (100)
	Uterus	0	0	1 (100)
Male	Penis	0	6 (26)	17 (74)
	Scrotum	3 (33)	1 (11)	5 (56)
	Testis	0	3 (50)	3 (50)
	Spermatic cord	0	3 (50)	3 (50)
	Prostate	0	1 (33)	2 (66)

3.4 Histology

For 36/47 (77%) of male patients and 211/461 (46%) of female patients included in this study, histology of the primary CRC was reported. 231/247 (94%) were simple adenocarcinomas. The remaining 16 patients with ovarian metastases had primary cancers consistent with either mucinous or signet ring carcinomas or neuro-endocrine cancers.

All studies that reported the histopathological findings from the metastases were consistent with spread from the primary colorectal cancer.

3.5 Primary tumour location

The location of the primary colorectal tumour was specified in 344/461 (75%) and 44/47 (94%) of the male and female patients, respectively. See Table 4.

Patients with ovarian metastases demonstrated a variety of primary tumour locations with no demonstrable trend towards any one location. 34% of ovarian metastases were associated with a primary tumour which had arisen in the sigmoid or rectum.

This is in contrast to lower genital tract (cervix, vagina, vulva) lesions in females which demonstrate a trend towards rectosigmoid primary lesions (50%, 100%, 86% respectively). Similarly, in men, the rectosigmoid is the most common location for a primary tumour in all metastatic sites (penis 100%, scrotum 78%, prostate 66%) with the possible exception of spermatic cord (50%) and testicular metastases (50%).

Table 5
– Summary of primary tumour location in the colon and rectum

		Total	ns (%)	Caecum (%)	Asc. Colon (%)	Trnsv. Colon (%)	Dsc. Colon (%)	Sigmoid colon (%)	Rectum (%)
Female	Ovary	438	115 (26)	23(5)	67(15)	17(4)	68(16)	84(19)	64(15)
	Vagina	10	0	0	0	0	0	5 (50)	5(50)
	Vulva	7	0	0	1(14)	0	0	2(29)	4(57)
	Cervix	4	1(25)	0	1(25)	0	0	2(50)	0
	Fallopian tube	1	1(100)	0	0	0	0	0	0
	Uterus	1	0	0	0	0	0	0	1(100)
Male	Penis	23	0	0	0	0	0	3(13)	20(87)
	Scrotum	9	1(11)	0	1(11)	0	0	0	7(78)
	Testis	6	2(33)	0	1(16)	0	0	2(33)	1(16)
	Spermatic cord	6	0	1(17)	0	0	2(33)	3(50)	0
	Prostate	3	0	1(33)	0	0	0	1(33)	1(33)
ns - not specified, Asc. - Ascending, Trnsv. - Transverse, Dsc. - Descending									

3.6 Staging of primary tumour

Table 5 displays a summary of primary tumour staging. For synchronous tumours, nodal status of the colorectal cancer was reported for 119/321 (37%) patients. These patients demonstrate an association with locally advanced colorectal tumours. 89/119 (75%) of patients had nodal disease within the mesorectum at time of surgery and 30/119 (25%) had isolated metastases with no nodal involvement.

In patients with metachronous lesions, nodal status was reported for 91/183 (49%) of patients. A similar association with advanced primary tumours was shown, with 67/91 (74%) patients having nodal disease confirmed by histopathologists after primary surgery.

For individual sites of metastasis this relationship is largely maintained with the possible exception of penile metastasis where the rate of T1-4N0M0 primary cancers is 47% (8/17)

TABLE 6 – Summary of primary tumour staging

		Synchronous				Metachronous						
		n=	N0	N1/2	ns	n=	N0	N1/2	ns	M0	M1	ns
Female	Ovary	299	27	83	189	139	9	45	85	3	2	134
	Vagina	7	2	2	3	3	1	2	0	3	0	0
	Vulva	1	0	1	0	5	1	2	2	3	1	1
	Cervix	0	n/a	n/a	n/a	4	0	3	1	3	0	1
	Fallopian tube	0	n/a	n/a	n/a	1	0	0	1	0	0	1
	Uterus	0	n/a	n/a	n/a	1	1	0	0	1	0	0
Male	Penis	6	0	1	5	17	8	8	1	15	0	2
	Scrotum	1	0	0	1	5	2	2	1	3	1	1
	Testis	3	0	1	2	3	1	2	0	2	1	0
	Spermatic cord	3	0	1	2	3	0	1	2	1	0	2
	Prostate	1	1	0	0	2	0	2	0	2	0	0

3.7 Treatment

Treatment offered for metastatic disease was classified as either curative intent or palliative intent and was specified in a total 44 of 47 (94%) of male patients and 387 of 461 (84%) of females.

For these patients, the rates of palliative intent treatment were 74% (17/22), 100% (6/6), 57% (4/7), 33% (2/6) and 33% (1/3) for penile, scrotal, testicular, spermatic cord and prostatic metastases respectively and 68% for all male patients.

For female patients, the palliative intent treatment rates were 37% (135/367), 0% (0/9), 17% (1/6), 33% (1/3), 0% (0/1) and 100% (1/1) for ovarian, vaginal, vulvar, cervical, salpingeal and uterine lesions, respectively and 39% for all females.

Overall, palliative intent treatment was provided for 38% (168/431) of patients.

3.8 Prognosis

Long-term outcome was reported on for 30/47 (64%) of male patients and 245/461 (53%) of female patients.

For male reproductive tract metastases prognosis was very poor. 80% (24/30) of patients were reported as having died, with 23 of these patients dying within the first year after diagnosis of metastatic disease and the remaining patient dying at 18 months. Of the 6 living patients just one was confirmed to be alive at 5 years after diagnosis which was a patient with a penile metastasis reported in 1950. 5 further patients were reported as alive at time of publication but follow-up time was limited to 6, 12, 16, 18 and 30 months.

In female patients, 66% (162/245) were reported as having died within 5 years with 2 further deaths occurring at unspecified times. However, 41 (17%) patients were reported as alive at or beyond 5 years and a further 40 patients were alive with a median follow-up time of 24 (1-54) months. Of the patients alive at 5 years, all were patients with ovarian metastases and had received surgical treatment.

4. Discussion

In this review, the ovaries were the most frequently encountered site for metastases and demonstrated the largest patient population. Ovarian metastases (OM) are reportedly found in 3-5%¹⁷ of patients with colorectal cancers and as such represent the most common site of spread explored in this review. Thus, they are likely the best understood. They are found largely in pre-menopausal women with advanced colonic cancers^{107, 108} as either synchronous or metachronous presentations. The optimal treatment remains controversial. One study examines the role of prophylactic oophorectomy at the time initial cancer resection¹⁰⁹. However, the negative effects of oophorectomy in pre-menopausal women including hormonal, metabolic and psychological consequences and inferior long-term overall survival are now well understood¹¹⁰ and prophylactic surgery is not routinely practiced. Oophorectomy is indicated in confirmed metastases and has been reported to have reasonable outcomes with 5 year and 10 year overall survival rates of 14% and 5% respectively¹⁷. This review confirms OMs are associated with the best prognosis of reproductive tract metastases and the suitability for potential curative surgery likely accounts for this finding.

In contrast to this, all sites of metastatic disease in men are associated with a dismal prognosis with just one patient (2%) surviving for 5 years. Although poorly reported in the source material, these patients tended to have advanced disease on presentation and as such were largely treated with palliative intent. In those patients who did have potentially curative treatment, they commonly had metastatic disease elsewhere and succumbed rapidly to their disease.

With the exception of gonadal disease, reproductive tract metastases are more likely to arise from rectal than colonic primaries. Several authors suggest various methods of spread for genital metastases including implantation during surgery, retrograde spread to the pudendal venous system or from obstructed inguinal or hypogastric lymphatic channels^{47, 56, 63}. The tendency for ovarian and possibly testicular metastases to arise from colonic primaries suggests an alternative dissemination pathway such as transcoelomic spread.

The rarity of these cases means the source material for this review is limited to case reports and cases series. As such, the review is descriptive only and no comparative analysis is possible. Furthermore, such reports are inherently subject to significant selection bias and cannot be considered to be representative of CRC reproductive tract metastases as a whole.

However, this review is the largest and most up-to-date summary of these unusual cases. Undoubtedly, patients with CRC metastases to the reproductive system have a very poor prognosis and often suffer from advanced and disseminated malignancy. However, there is evidence of long-term survival in selected patients after surgical treatment. Perhaps one way to learn more about these rare occurrences with worse prognosis is through establishing registries that include such patients. This would provide a hub for advancing clinical care and research into this area and further our understanding of these rarities. Proteomics, genomics and metabolomics of these unusual metastases would shed more light on pathogenesis and perhaps, help us to improve outcomes of such patients in future.

Declarations

Conflicts of Interest and Source of Funding: None to declare

Author Contributions

JA – Literature search, Data collection, Data management, Data analysis and manuscript writing

JW – Literature search, Data Analysis, Manuscript writing

AA – Literature search, Data collection

RW – Literature search, Data collection

GTW – Literature search, Data collection

SA – Manuscript editing

KA – Protocol and project development, Data analysis, Manuscript editing

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The authors declare that they have no conflict of interest

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Figures

Figure 1

PRISMA diagram of systematic search and study selection