American Journal of Men's Health
July-August 1–13

DOI: 10.1177/15579883211044881
journals.sagepub.com/home/jmh
SAGE

Multiple Primary Tumors Originating From the Prostate and Colorectum A Clinical-Pathological and Therapeutic Challenge

Sorin Dema[1], Andreea Bota[2], Sorina Maria Tăban[2], Adelina Gheju[2], Alis Liliana Carmen Dema[2], Alexei Croitor[3], Robert Alexandru Barna[2,4], Oana Popa[2], Răzvan Bardan[5], and Alin-Adrian Cumpănaş[5]

Abstract

Considering that the incidence of colorectal (CRC) and prostatic cancer (PC) increases with age, metachronous and synchronous tumors can often affect the same patient. Despite the importance of this subject for the diagnosis and management of oncologic patients, in medical literature the data are scarce. The aim of the study was to evaluate the incidence and the characteristics of double/multiple primary malignant tumors (D/MPMTs) with colorectal and prostatic origin, in patients admitted to a reference hospital in West Romania. A 4-year retrospective observational study (2016–2019) was conducted by analyzing the medical records of all patients admitted in the hospital. Demographic and clinical data, as well as tumor-related parameters, were extracted. We identified 413 consecutive hospitalized patients with PC, and 21 (5%) of them also had a primary CRC. At the time of diagnosis, the mean age of the patients with PC was 71.2 ± 6 years, and 71.8 ± 10 years for patients with CRC. Synchronous PC and CRC tumors were identified in 3/21 cases and metachronous tumors in 18/21 cases. Prostate cancer was the first tumor to be diagnosed in 13/18 cases and CRC in 5/18 cases. The most frequent subtype of PC was acinar adenocarcinoma (90%) and for CRC cases, conventional adenocarcinoma (90%). Prostate and colorectal cancers tend to co-occur in a single patient. The diagnosis of one of these two types of tumors should imply the screening for the other one, because these patients require a multidisciplinary and personalized approach.

Keywords

prostate cancer, colorectal cancer, multiple primary malignant tumors, synchronous tumors, metachronous tumors

Received June 6, 2021; revised August 12, 2021; accepted August 18, 2021

Introduction

The incidence of prostate cancer (PC) and colorectal cancer (CRC) increases with age (Nash et al., 2012), PC being diagnosed at a mean age of 66 years, while CRC at a mean age of 65 years (Rawla, 2019; Rawla et al., 2019). The last two–three decades have brought an improvement in the survival of patients diagnosed with PC and CRC due to the early detection of neoplasms through screening programs, to refining diagnostic techniques and to the use of new therapies (Das, 2017; Herrmann et al., 2013; Howe, 2003; Vogt et al., 2017). For these reasons, to which is added the increasing knowledge of the phenomenon of double/multiple primary malignant tumors (D/MPMTs), it should come as no surprise that PC and CRC could be identified in the same patient, in a synchronous or metachronous manner.

The incidence of D/MPMTs in which one of the tumors was PC varies between 1.14% (Jin et al., 2014) and 8.7% (Weir et al., 2013), while the cases in which one of the multiple tumors was a CRC had an incidence up to 19.9% (Halamkova et al., 2021). A Dutch study that included almost 430,000 patients diagnosed with at least one form of cancer reported a prevalence of 7% for multiple malignancies, and 0.3% for the association of PC with CRC (L. Liu et al., 2011). If we take into account

only the association of PC with rectal cancer, the incidence varied between 0.4% and 0.5 % (Kavanagh et al., 2012; Sturludóttir et al., 2015), increasing to 1% for PC and rectosigmoid cancer (Jacobs et al., 2020). These cases represent a challenge for the physicians who manage them.

The present work started from the observation that some patients were diagnosed, simultaneously or after a certain interval of time, with CRC and PC, with sometimes unusual situations in which one of the tumors was diagnosed, in the case of synchronous tumors. Given that the issue of D/MPMTs is becoming increasingly important and relevant and that, to our knowledge, in the medical literature the data on this association are scarce, this study aimed to analyze cases of D/MPMTs with colorectal and prostatic origin, in a retrospective observational study that covered a time interval of 4 years.

Materials and Methods

The present study was performed in line with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Emergency County Hospital Timisoara (34/19.08.2020). The data collected retrospectively did not contain personal information; therefore, there was no need of informed consent to participate.

First, we identified all patients diagnosed with PC in the Urology and Pathology departments of the Emergency County Hospital from Timisoara (SCJUPBT), over the time span of 2016–2019. "Prostate cancer," "prostatic cancer," and "prostatic adenocarcinoma" were the keywords used to search the database.

In the cohort of patients identified with PC, we searched those patients who also had a diagnosis of CRC. "Colon carcinoma," "rectal carcinoma," "colorectal carcinoma," and "colorectal adenocarcinoma" were the keywords used to search in patient's personal history and hospital records of those patients identified with PC.

The inclusion criteria were male patients with PC diagnosed in our hospital between 2016 and 2019, who also had a diagnosis of CRC. The exclusion criteria were the cases in which one of the tumors turned out to be benign, and CRC or PC diagnosed at autopsy.

For all these cases, the following data were extracted from the patient's medical record: for PC—date of diagnosis, age at the time of the diagnosis, the blood level of prostate-specific antigen (PSA) at diagnosis, the type of specimen in which PC was diagnosed (core-needle biopsy [CNB], transurethral resection of the prostate [TURP], radical prostatectomy [RP], or other specimens); the Gleason score (GS), grade group (GG), the most advanced stage determined throughout the course of the disease, for cases where this was possible, according to American Joint Committee on Cancer (AJCC)—Tumor, Lymph Nodes, Metastases (TNM) classification, 7th (Edge et al., 2010) and 8th edition (Amin et al., 2017); for CRC—date of diagnosis, age at the time of the diagnosis, number and location of colorectal tumors, histologic subtype, tumor grade (G), pathologic stage (pTNM), according to AJCC TNM classification, 7th (Edge et al., 2010) and 8th (Amin et al., 2017) edition. Right-sided tumors were considered tumors originating proximally to the splenic flexure (from caecum, ascending colon, transverse colon), whereas left-sided tumors were considered tumors originating from the descending colon, sigmoid, and rectum (Iacopetta, 2002). Statistical analysis was performed using Excel software (Microsoft Office 365 Suite).

To classify tumors as D/MPMTs, we used Warren and Gates' criteria (Warren, 1932): (a) each tumor should be malignant, (b) each tumor should be histologically distinct, (c) the possibility that one is metastasis of the other must be excluded. Two or more neoplasms identified simultaneously within the same patient or within 6 months after the initial diagnosis were considered synchronous cancers, while metachronous tumors were defined as cancers occurring more than 6 months apart (Das, 2017; Lv et al., 2017). Metachronous tumors were further subclassified as early if has occurred within the first 3 years after the initial tumor, and as late if they occurred after 3 years (Chen & Sheen-Chen, 2000).

[1]Radiotherapy Service, Emergency City Hospital Timisoara, Timisoara, Romania
[2]Department II Microscopic Morphology—Discipline of Morphopathology, "Anapatmol" Research Center, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[3]Urology Department, Emergency County Hospital Timisoara, Timisoara, Romania
[4]Department of Internal Medicine II—Discipline of Gastroenterology and Hepatology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[5]Department of Orthopedic Surgery—Traumatology—Urology—Medical Imaging—Urology Department, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Corresponding Author:
Robert Alexandru Barna, Department of Internal Medicine II—Discipline of Gastroenterology, "Victor Babes" University of Medicine and Pharmacy, No. 2 Eftimie Murgu Sq, Timisoara, Timis 300041 Romania.
Email: robert.barna@umft.ro

Results

From a total of 413 patients with PC identified from the database of SCJUPBT between 2016 to 2019, 21 patients (5%) also had CRC. Epidemiological and pathological characteristics of the patients are presented in Tables 1 and 2.

At the time of PC diagnosis, patients were aged between 53 and 80 years with a mean age of 71.2 years (standard deviation [SD]: 6 years), and at the time of CRC diagnosis, patients were aged between 39 and 86 years with a mean age of 71.8 years (SD: 10 years).

The majority of cases (18 cases—85.7%) were metachronous tumors, and only three cases (14.3%) synchronous tumors. The 18 metachronous tumors were then classified as "early metachronous tumors"—nine cases (50%), with a mean time span of 23.6 months (SD: 9 months) between the diagnosis of the two tumor types (7–36 months) and "late metachronous tumors"—nine cases (50%) with a mean time interval of 110.6 months (SD: 101 months) between the diagnosis of the two tumor types (52–374 months). Among these patients, PC was the first tumor to be diagnosed in 13/18 cases (72.2%), while CRC was the first tumor in 5/18 cases (27.8%). Among 18 patients with metachronous tumors, six underwent RT for PC. Information regarding the treatment of PC was not available for 12 patients. In the synchronous tumor group (three cases), the mean age at the time of diagnosis was 67.3 years (SD: 6.2 years), and the interval between the two diagnoses was between 1 month and 5 months long, with an average of 3 months. In two of the D/MPMT cases identified in our study, one synchronous and one metachronous, PC was reported in the rectal resection specimen as a tumor invading the outer layers of the rectal wall, in the synchronous case with metastatic involvement of two perirectal lymph nodes. Neither of these two cases had serum PSA determined before surgery and in both cases the Gleason score was 9.

PC diagnosis was histologically confirmed in 14 cases by CNB, in five cases by TURP, in one case in rectal resection specimen, and for one case this information was not available. Serum PSA level was 8.4–60 ng/ml at the time of the diagnosis, with a mean value of 29.5 ng/ml (SD: 16 ng/ml). In nine out of the 21 patients from our research, PSA levels were not registered. Nine cases of PC could be staged and were classified as follows: three cases—stage I and six cases—stage III–IV.

Out of the 21 PC cases, 20 were acinar type and only one case had an association of acinar and ductal adenocarcinoma. The Gleason score ranged between 6 and 10, with a mean value of 7.5 and we noticed the following distribution regarding the grade groups: two cases—grade group I, 10 cases—grade group II, one case—grade group III, one case—grade group IV, five cases—grade group V (four cases with Gleason score 9 and one case with Gleason score 10). The patient with PC with mixed histological features had a Gleason score of 7 (3+4)/grade group 2 for the acinar component and a Gleason score of 8 (4+4)/grade group 4 for the ductal component of adenocarcinoma. For one patient who was diagnosed with PC in another hospital, Gleason score and grade group were not available.

Regarding the CRC, in four cases the carcinoma was located in the right colon (the ascending and transverse colon, each with two cases), and in 17 cases the left colon was affected, including five cases of rectal carcinoma. Four of the 21 patients with CRC and PC had more than two primary malignant tumors as follows: one patient, suspected of Lynch syndrome, apart from PC had three metachronous colon cancers (two in the left colon and one in the right colon); two patients presented each two synchronous CRC (for one case both tumors involved the left colon, and for the other case, tumors developed in the left colon and rectum) in association with PC; and the last patient was diagnosed with CRC, PC, and high-grade papillary urothelial cancer of the urinary bladder.

The vast majority of CRC was adenocarcinomas not otherwise specified (ADK NOS) (18 cases), a single tumor was mucinous adenocarcinoma, and two patients presented each two synchronous colonic tumors: mucinous adenocarcinoma and ADK NOS, respectively, two ADK NOS. Considering tumor grade, most CRC (16 cases) were moderately differentiated (G2), two tumors were poorly differentiated (G3), and one tumor was well differentiated (G1). Two out of the three cases with double/multiple colon carcinomas were scored differently for each intestinal tumor: G2 and G3, respectively, G1 and G2. Concerning the depth of intestinal wall infiltration, two cases were pT1, four cases pT2, seven cases pT3, and six cases pT4. For one out of the two cases with synchronous CRC, intestinal tumors were evaluated as pT1 and pT2 and for the other one, both tumors were pT4a. After lymph node assessment, 12 cases were classified as pN0, four pN1, four pN2, and one case as pNx (no information regarding lymph node status was available for the case of malignant polyp).

In conclusion, all cases of CRC were classified as follows: four stage I, seven stage II, five stage III, and two stage IV tumors. The two cases with double primary tumors (DPTs) of the colon were reported based on the most advanced stage, resulting one stage II and one stage III tumor. The only case with no information regarding the lymph node involvement was not staged. Fifteen of the 21 patients were alive at the study endpoint, while six patients were deceased.

Discussion

The incidence of D/MPMTs has risen in the last decades (Testori et al., 2015; Vogt et al., 2017), being reported in

Table 1. Main Characteristics of the Patients Included in the Study.

Patient Characteristics		1	2	3*	4	5	6	7*
Synchronous or metachronous		S	S	S	M	M	M	M
Time interval between tumor diagnosis		1 month	5 months	3 months	NA	27 months	113 months	21 months
PC	**Age**	69	59	74	71	79	65	77
	PSA	45	13.4	NA	NA	28.9	NA	8.76
	Procedure	TURP	CNB	Partial prostatectomy	NA	CNB	CNB	CNB
	Histology	Acinar ADK	Acinar ADK	Acinar ADK	NA	Acinar ADK	Acinar ADK	Acinar ADK
	GS	3+4	3+4	4+5	NA	3+4	3+4	3+4
	GG	2	2	5	NA	2	2	2
	TNM	T1b	pT3a	pT4N1	NA	NA	T2c	NA
	Treatment	NA	RP followed by RT	NA	RT	AS	RP followed by RT	NA
CRC	**Age**	69	59	74	75	82	74	75
	Tumor site	Left colon	Rectum	Rectum	Left colon	Left colon	Left colon	Left colon
	Procedure	Hartmann Procedure	Low anterior resection	Abdominoperineal Resection	Left hemicolectomy	Sigmoidectomy	Sigmoidectomy	Left hemicolectomy
	Histology	ADK Mucinous	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS
	TNM	pT4aN1bM1c	pT1N1a	pT2N0	pT4aN1b	pT4aN2aM1c	pT2N0	pT3N0
	Histologic grade	3	1	2	2	2	2	2

(continued)

Table 1. (continued)

Patient Characteristics		8	9	10	11	12	13*	14*
Synchronous or metachronous		M	M	M	M	M	M	M
Time interval between tumor diagnosis		52 Months	60 Months	100 Months	63 Months	36 Months	27 Months	7 Months
PC	**Age**	72	74	67	53	72	70	68
	PSA	NA	8.44	NA	44	NA	12.6	36.34
	Procedure	TURP	CNB	CNB	CNB	TURP	CNB	CNB
	Histology	Acinar ADK	Acinar ADK	Acinar ADK	Acinar ADK	NA	Acinar ADK	Acinar ADK
	GS	3+4	3+4	2+4	3+3	3+4	3+4	3+4
	GG	2	2	1	1	2	2	2
	TNM	T1b	NA	NA	pT3b	NA	NA	NA
	Treatment	AS	RT	RT and AS	RP	RT	NA	NA
CRC	**Age**	76	78	74	59	76	67	67
	Tumor site	Left colon	Left colon	Rectum	Left colon	Right colon	Right colon	Right colon
	Procedure	Low anterior resection	Hartmann Procedure	Laparoscopic rectal amputation	Hartmann Procedure	Right hemicolectomy	Right hemicolectomy	Right hemicolectomy
	Histology	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS
	TNM	pT3N0	pT3N2a	pT2N0	pT4aN2a	pT3N0	pT3N0	pT4aN0
	Histologic grade	2	2	2	2	2	3	2

(continued)

Table 1. (continued)

Patient Characteristics		15*	16	17	18	19	20	21*
Synchronous or metachronous		M	M	M	M	M	M	M
Time interval between tumor diagnosis		60 Months	18 Months	28 Months	12 Months	36 Months	63 Months	374 Months
PC	**Age**	77	66	79	74	79	80	70
	PSA	18	NA	NA	46.75	NA	32	60
	Procedure	CNB	TURP	CNB	CNB	TURP	CNB	CNB
	Histology	Acinar ADK	Acinar ADK	Acinar ADK	Acinar ADK Ductal ADK	Acinar ADK	Acinar ADK	Acinar ADK
	GS	4+5	4+3	5+5	3+4 (acinar) 4+4 (ductal)	4+4	5+4	4+5
	GG	5	3	5	2 (acinar) 4 (ductal)	4	5	5
	TNM	NA	T1b	NA	NA	pT4	pT4	Na
	Treatment	NA	NA	RT	NA	NA	AS	NA
CRC	**Age**	72	67	81	75	82	86	39
	Tumor site	Rectum	Rectum	Right colon	Left colon	Left colon Distal Rectum	Left colon	Left colon
	Procedure	Low anterior resection	Polypectomy	Right hemicolectomy	Low anterior resection	Sigmoidectomy	Left hemicolectomy	Left hemicolectomy
	Histology	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS	ADK NOS ADK Mucinous	ADK NOS
	TNM	pT3N0	pT1	pT4aN1b	pT3N0	Left colon: pT2N0 Distal Rectum: pT1N0	ADK NOS: pT4a ADK Mucinous: pT4aN2b	pT2N0
	Histologic grade	2	2	2	2	Left Colon: 1 Distal Rectum: 2	ADK NOS: 2 ADK Mucinous: 3	2

Note. S = synchronous; M = metachronous; PC = prostate cancer; PSA = prostatic-specific antigen; GS = Gleason score; GG = grade group; CNB = core needle biopsy; TURP = transurethral resection of the prostate; ADK = adenocarcinoma; RP = radical prostatectomy; RT = radiotherapy; AS = androgenic suppression; CRC = colorectal cancer; NA = not available. *CRC was the first tumor diagnosed.

Table 2. Summary of the Results.

Parameter		Results
Lot no.		413 patients with PC
Total no. of patients with D/MPMT: PC and CRC (%)		21 patients (5%)
Synchronous tumors:		3 cases
Metachronous tumors:		18 cases
PC diagnosed first		13/18 patients
CRC diagnosed first		5/18 patients
PC	Mean (± SD) age at the time of diagnosis	71.2 ± 6 years
	Mean (± SD) PSA value	29.5 ± 16
	Diagnostic procedure	14 CNB 5 TURP 1 rectal resection specimen 1 undetermined
	Mean Gleason score (± SD)*	7.5 ± 1
	Group grade*	2 grade group I 10 grade group II 1 grade group III 1 grade group IV 5 grade group V
	Stage	3 stage I 6 stage III-IV 12 cases were not pathologically staged
CRC	Mean (± SD) age at the time of diagnosis	71.8 ± 10 years
	Tumor site	4 right colon 17 left colon (5 rectal carcinoma)
	Histologic grade	1 well differentiated (G1) 16 moderately differentiated (G2) 2 poorly differentiated (G3) 2 cases with double colon carcinomas (G1 & G2, respectively G2 & G3)
	Stage	4 stage I 8 stage II 6 stage III 2 stage IV 1 case could not be staged

Note. *One patient had two histologic patterns of prostate carcinoma, one with Gleason score 7 (grade group II) and one with Gleason score 8 (grade group IV). For another patient, we did not know the Gleason score.
D/MPMT = double multiple primary malignant tumor; PC = prostate cancer; CRC = colorectal cancer; SD = standard deviation; CNB = core needle biopsy; TURP = transurethral resection of the prostate.

the range of 2%–17% of cases by some authors (Vogt et al., 2017). The rate of multiple tumors is up to 40% higher if the analysis targets specialized oncology centers (Howe, 2003), where the follow-up of patients already diagnosed with a malignant tumor is more rigorous.

Our focus lies not in analyzing the general D/MPMTs incidence, but the D/MPMT cases where PC and CRC have been diagnosed in the same patient. We chose to study these two types of cancer because they are among the most frequent neoplasms diagnosed in male population, following lung cancer, in Romania and in the majority of developed countries (Ferlay et al., n.d.) and due to the observation that these two types of tumors tend to co-occur within the same patient. This association requires a particular management of the patient in order to identify a therapeutic strategy to cover both forms of tumors, without unacceptable side effects (Vogt et al., 2017).

The incidence of D/MPMTs with prostate and colorectal origin varies considerably depending on the inclusion criteria, the size and characteristics of the cohort, the involved anatomical region of the large bowel, and the length of the follow-up (Table 3) (Jacobs et al., 2020; Kavanagh et al., 2012; L. Liu et al., 2011; Sturludóttir et al., 2015). Compared with Sturludóttir et al., who analyzed the association between PC and rectal cancer over a period of 16 years, Jacobs et al. reported a twofold higher incidence for synchronous PC and rectosigmoid cancer over a period of 20 years (Jacobs et al., 2020; Sturludóttir

Table 3. Summary of the Previously Published Articles Cited in This Paper, Which Address the Issue of Multiple Primary Malignant Tumors With Prostate and Colorectal Origin.

Authors	Year of Publication	No. of Patients Included	No. (%) of Patients With Multiple PC and CRC	No. (%) of Synchronous cases	No. (%) of Metachronous Cases	Classification Used for Synchronous and Metachronous Tumors
Terris & Wren	2001	20	4 (20%)	3 (75%)	1 (25%)	NA
Murray et al.	2004	112	5 (4.5%)	NA	NA	NA
Mourra et al.	2005	234	3 (1.3%)	1 (33%)	2 (66%)	NA
Hoffman et al.	2008	29,266	1,710 (5.8%)	NA	NA	SEER
Nieder et al.	2008	243,082	883 (0.3%)	NA	NA	SEER
Rapiti et al.	2008	1,134	19 (1.6%)	NA	NA	IARC
Lin et al.*	2011	3	3	3	0	NA
Liu et al.	2011	424,340	1,547 (0.3%)	NA	NA	IARC
Kavanagh et al.#	2012	3,425	12 (0.4%)	9 (75%)	3 (25%)	3 months interval
Sharp et al.	2012	451	18 (3.9%)	5 (27%)	13 (73%)	NA
Van Hemelrijck#	2012	72,613	1,368 (1.9%)	3 (0.3%)	1,365 (99.7%)	SEER
Sturludottir et al.#	2015	29,849	157 (0.5%)	29 (18%)	128 (82%)	NA
Testori et al.*	2015	1	1	1	0	6 months interval
Kamiyama et al.*	2016	1	1	1	0	NA
Villegas-Otiniano et al.*	2018	1	1	1	0	NA
Jacobs et al.	2020	31,883	330 (1%)	54 (16%)	276 (84%)	12 months interval
Halamkova et al.	2021	1,174	28 (2.3%)	7 (25%)	21 (75%)	6 months interval

Note. Studies marked with * are case reports or case report series.
For studies marked with #, the numbers represent only cases of colon or rectal cancer.
NA = not available; PC = prostate cancer; CRC = colorectal cancer; SEER = Surveillance, Epidemiology, and End Results program; IARC = International Agency for Research on Cancer.

et al., 2015). Another study from Czech Republic showed that 2.3% of patients diagnosed with CRC between 2003 and 2013 and followed until 2018 developed PC (Halamkova et al., 2021), in line with a Swedish study that has shown that 1.9% of those over 72,000 patients have associated colon cancer and PC (Van Hemelrijck et al., 2012). The incidence of 5% for D/MPMTs identified in our study is significantly higher compared with the aforementioned studies.

First described by Billroth in 1889 (Billroth, 1889) and then defined by Warren and Gates (Warren, 1932), D/MPMTs can be divided into two categories: (a) synchronous, meaning the cancers occur simultaneously (within 2 months according to the SEER definition) (SEER, 1998); and (b) metachronous, with the cancers following a subsequent path (more than 2 months apart). Another classification system suggest a time frame of 6 months (Das, 2017; Lv et al., 2017) or even 12 months (Jacobs et al., 2020) to separate the two tumor categories. We chose the 6-month time frame to differentiate the synchronous tumors from the metachronous ones and the 3-year period to separate the early metachronous from the late ones.

In our case series, we identified a significantly higher metachronous tumor percentage than the synchronous one (85.7% vs. 14.3%), with an initial PC diagnosis in 72.2% of the cases, in accordance with other literature data that reported that the ratio of synchronous to metachronous tumors is definitely in favor of the metachronous ones, regardless of the location of the tumors (Tziris et al., 2008). If it is to be referred strictly to metachronous prostate and colorectal tumors, Jacobs et al. (2020) noticed that most cases of D/MPMTs (84%) with one of the tumors being PC and the second one being rectosigmoid cancer were metachronous tumors, with the PC tumor being the first one detected more frequently (59% of the cases) (Jacobs et al., 2020).

Double/multiple primary malignant tumors in which PC co-occurred with CRC were the most common association in the group of synchronous tumors (26%) in a Spanish study from 2010 (las Heras Alonso & Gelabert Mas, 2010), and it is estimated that they will be more and more common with the prolongation of life expectancy and the improvement of diagnostic methods for the two neoplasms (Seretis et al., 2014). In another study, Kavanagh et al. analyzed 2,580 PC and 845 rectal cancer cases over a period of 11 years and reported that 75% of cases with double primary cancers of prostate and rectum were synchronous tumors (Kavanagh et al., 2012). This aspect was noted in our study as well, where 66.67% of the synchronous cases associated PC with rectal cancer.

Terris and Wren (2001) reported that about one-sixth of patients over the age of 50 and life expectancy greater than 10 years, diagnosed with rectal cancer, have been

identified with synchronous PC by screening for this neoplasia. This aspect suggest that all patients diagnosed with rectal cancer should be carefully investigated for a possible synchronous PC because treating rectal cancer by anterior abdominoperineal resection (APR) makes digital rectal examination (DRE) or transrectal CNB of the prostate impossible, requiring a transperineal approach, which is much more difficult (Murray et al., 2004). Furthermore, considering the observations of Sharp et al. (2012), that over 3% of newly diagnosed PC patients have asymptomatic synchronous CRC, screening colonoscopy in patients with PC seems indicated, especially if they have not had such an investigation in the last 3 years.

To establish the correct diagnosis of colorectal and prostate synchronous malignant primary tumors is much more complicated than that of metachronous tumors, from several points of view. The most important is the documentation of the two types of tumors, as there are cases of PC that have infiltrated the rectum, misdiagnosed as rectal tumors, and implicitly as synchronous tumors (Bowrey et al., 2003). There is the opposite situation, when CRC invades the prostate (Osunkoya et al., 2007), being diagnosed as a primary prostate tumor. For the diagnosis of synchronous CRC and PC, imaging and paraclinical investigations are of real use. It is estimated that routine staging by magnetic resonance imaging (MRI) for patients with rectal cancer will diagnose more patients with PC and consequently increasing numbers of patients with synchronous PC and rectal cancer (Kavanagh et al., 2012). In addition, serum levels of carcinoembryonic antigen (CEA) and PSA are useful for detection/confirmation and for the follow-up of the CRC and PC, respectively, with the mention that the marker associated with one tumor may increase secondary to RT administered for the other one (Gripp et al., 2000; Nash et al., 2012) and that direct invasion of the prostate by rectal cancer could increase serum PSA level (Lin et al., 2011). Serum PSA was not determined before surgery in the two cases from our study, where poorly differentiated PC invaded the rectal wall. In these cases, PC was not clinically suspected, but if PSA levels would have been measured, a suspicion of a PC could have been raised. In one of these two cases, PC was detected incidentally, during the histopathological examination of the rectal resection specimen, as a tumor infiltrating from the outer layers of the rectal wall, aspects reported by other authors as well (Mourra et al., 2005; Murray et al., 2004). Bowrey et al. (Bowrey et al., 2003) noticed that in only two out of the six cases of rectal invasion by PC, the PC was suspected when the patient presented with digestive symptoms. For the two cases in which PCs invaded the colorectal wall, Gleason score was 9, in accordance with other data reporting that most PC invading the colorectum are generally poorly differentiated, with a Gleason score between 8 and 10 (Lane et al., 2008).

The invasion of the rectum by a PC is reported at varying rates, from 0.1% (Tang et al., 2017) to 4% and even up to 12% (Bowrey et al., 2003), with higher values in autopsy studies (Arnheim, 1948). The rectal involvement in PC can occur via several routes: through direct invasion into the rectum through Denonvilliers fascia (Abbas et al., 2011), through lymphatic vessels (Murray et al., 2004), through hematogenous metastasis (Z. H. Liu et al., 2015), or through an extremely uncommon way—implantation of PC cells during the transrectal CNB of the prostate (Vaghefi et al., 2005). The extension of the PC to the perirectal lymph nodes, documented in our study in one of the simultaneous synchronous tumor cases, with the invasion of the rectum by PC, can influence the staging and management of the two neoplasms. In this regard, in their study, Murray et al. (2004), who analyzed 112 cases of rectal cancer with lymph node metastases diagnosed within 10 years, identified five patients (4.5%) with PC metastases in the perirectal lymph nodes, metastases which in 40% of cases were erroneously attributed to rectal adenocarcinomas. The clinical data (symptomatology, history, local examination), the value of some serum markers (PSA, CEA), the ratio of free PSA/total PSA (Z. H. Liu et al., 2015; Tang et al., 2017), and the IHC reactions are really useful in the aforementioned situations.

CRC and PC benefit from screening programs in some countries (Sirovich et al., 2003), but not in Romania, and, as a consequence, the respective tumors are detected at a more advanced stage, especially PC, which begins, as a rule, in the peripheral postero-lateral area of the gland and produces symptoms later on (McNeal et al., 1988). In our study, six of the nine cases of PC that could be staged based on histopathological examination were classified as stage III-IV. The high average value of serum PSA level (29.5 ng/ml) for the cases in which this parameter was known suggests an advanced stage of PC, based on already demonstrated correlation between the value of serum PSA and the PC stage (Bangma et al., 1997). By contrast, only 8/21 (38%) cases of CRC from our study were stage III-IV tumors, possibly related to the high number of tumors located in the left colon (17/21 - 81%), tumors that according to Hemminki et al. (2010) are diagnosed in less advanced stages than those developed in the right colon.

In terms of treatment, the presence of D/MPMTs may influence the treatment. The treatment of D/MPT is a challenge for the medical team and depends on the synchronous or metachronous character of the tumors, on the age, comorbidities and preference of patients, the stage of the tumors, and the equipment of the hospital (Colonias et al., 2005; Hoffman et al., 2008; Nash et al., 2012). Treating one of the two tumor types (PC and

CRC), particularly with RT, could influence the diagnosis, treatment, or could even raise the risk for a secondary tumor (Nash et al., 2012). Regarding the diagnostic problems, in radiation colitis/proctitis secondary to RT for PC, symptoms such as diarrhea and bleeding, as well as atypia induced in colonic/rectal epithelial and/or stromal cells, can be interpreted as the prerogative of a neoplastic process (Moore et al., 2020). In addition, prostate biopsy which can cause symptoms such as rectal discomfort and tenesmus that persists for several weeks may mimic rectal neoplasia (Nash et al., 2012). On the other hand, RT administered for rectal cancer can reduce the size or even cure an occult PC (Nash et al., 2012). Regarding the risk of developing a second tumor due to the treatment of the first one, some papers reported an increased risk of subsequent CRC in patients treated with external-beam RT for PC, the interval between irradiation and tumor occurrence being at least 5 years, but not for interstitial brachytherapy (Nieder et al., 2008; Rapiti et al., 2008; Wallis et al., 2016). However, this association was not confirmed by other studies, and there is no scientific consensus regarding carcinogenic effects of these treatments (Nash et al., 2012). In our study, among 18 patients with metachronous tumors, six underwent RT for PC, but the number is too small in order to draw a conclusion.

In the particular case of D/MPMT with one tumor originating in the prostate and the second one a CRC, the treatment must be planned in a multidisciplinary team, after an accurate diagnostic work-up and must be individualized, taking into account the location and stage of the tumors and the particularities of the case. For synchronous tumors of the rectum and prostate, there are several alternatives: surgical excision of both tumors using classical or laparoscopic-robotic approach, excision of the intestinal tumor and external beam radiation therapy (EBRT) for PC; EBRT for both tumors (rectal and prostatic), radio-chemotherapy followed by surgery for rectal cancer combined with hormone therapy or watchful waiting for PC (in selected cases) (Kamiyama et al., 2016; Lin et al., 2011).

This study has several noteworthy limitations. First, the study included a limited number of patients, which could not reflect the real incidence of this association. Second, the histopathological diagnosis, clinical stage, and treatment information were not available for all PC cases, which did not allow us to have a comprehensive analysis of all cases studied. Considering that the life expectancy continues to rise in most developed countries, the advantage of this study consists in raising awareness on clinical and morphological diagnostic problems, as well on therapeutic issues regarding the association of PC and CRC, among specialists involved in the management of these patients. Therefore, actions are required to allow the early identification of the second tumor, in order to choose the optimal therapy and to adapt it according to the existence, in antecedents or synchronous, of the first tumor, because the late diagnosis of any of the two types of tumors can change considerably the therapeutic approach of these patients.

Conclusion

To the best of our knowledge, this is the first series of Romanian patients with double/multiple primary PC and CRC. Although the study has some limitations, the incidence reported in our paper should not be neglected. This finding should raise awareness among urologists, general surgeons, radiologists, and pathologists that the association between PC and CRC within the same patient tend to co-occur, and from a diagnostic point of view, identifying one of these two tumors requires the screening for the other one. From the therapeutical point of view, this challenging association of PC and CRC needs a multidisciplinary and personalized approach, especially in the case of synchronous rectum and prostate malignancy.

Authors' contributions

SD, SMT, ALCD, RB, AAC contributed to the design and conception of the study. AB, AG, AC, RAB, OP participated in the acquisition and organization of the data. All authors analyzed and interpreted the data. Moreover, all authors were involved in selection, analysis, and interpretation of cited references. ALCD, AB, AC, RAB, OP prepared the original draft, and SD, SMT, AG, RB, AAC revised the manuscript critically for important intellectual content. SD, AB, ALCD, AC, RAB are responsible for the authenticity of all the raw data. All authors read and approved the final manuscript and all of them agreed to be accountable for all aspects of the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Alis Liliana Carmen Dema https://orcid.org/0000-0003-0767-2718

Robert Alexandru Barna https://orcid.org/0000-0003-4634-969X

References

Abbas, T. O., Al-Naimi, A. R., Yakoob, R. A., Al-Bozom, I. A., & Alobaidly, A. M. (2011). Prostate cancer metastases to the rectum: A case report. *World Journal of Surgical Oncology*, *9*(1), 56. https://doi.org/10.1186/1477-7819-9-56

Amin, M. B., Edge, S., Greene, F., Byrd, D. R., Brookland, R. K., Washington, M. K., Gershenwald, J. E., Compton, C. C., Hess, K. R., Sullivan, D. C., Jessup, J. M., Brierley, J. D., Gaspar, L. E., Schilsky, R. L., Balch, C. M., Winchester, D. P., Asare, E. A., & Madera, L. (2017). *AJCC cancer staging manual*, 8th ed. Springer.

Arnheim, F. K. (1948). Carcinoma of the prostate; a study of the postmortem findings in 176 cases. *The Journal of Urology*, *60*(4), 599–603. https://doi.org/10.1016/S0022-5347(17)69279-6

Bangma, C. H., Kranse, R., Blijenberg, B. G., & Schröder, F. H. (1997). The free-to-total serum prostate specific antigen ratio for staging prostate carcinoma. *Journal of Urology*, *157*(2), 544–547. https://doi.org/10.1016/S0022-5347(01)65197-8

Billroth, T. (1889). *Die allgemeine chirurgische Pathologie und Therapie in 51 Vorlesungen*. De Gruyter. https://doi.org/10.1515/9783111688145

Bowrey, D. J., Otter, M. I., & Billings, P. J. (2003). Rectal infiltration by prostatic adenocarcinoma: Report on six patients and review of the literature. *Annals of the Royal College of Surgeons of England*, *85*(6), 382–385. https://doi.org/10.1308/003588403322520726

Chen, H. S., & Sheen-Chen, S. M. (2000). Synchronous and "Early" metachronous colorectal adenocarcinoma: Analysis of prognosis and current trends. *Diseases of the Colon and Rectum*, *43*(8), 1093–1099. https://doi.org/10.1007/BF02236556

Colonias, A., Farinash, L., Miller, L., Jones, S., Medich, D. S., Greenberg, L., Miller, R., & Parda, D. S. (2005). Multidisciplinary treatment of synchronous primary rectal and prostate cancers. *Nature Clinical Practice Oncology*, *2*(5), 271–274. https://doi.org/10.1038/ncponc0173

Curtis, R., Freedman, D., Ron, E., Ries, L., Hacker, D., Edwards, B., Tucker, M., & Fraumeni, J. J. (Eds.). (2006). *New malignancies among cancer survivors: SEER Cancer Registries, 1973–2000*. National Cancer Institute, NIH.

Das, S. (2017). Synchronous and Metachronous cancers: An update. *Annals of Clinical Case Reports*, *2*, 1388. http://www.anncaserep.com/full-text/accr-v2-id1388.php

Edge, S., Byrd, D., Compton, C., Fritz, A., Greene, F., & Trotti, A. (Eds.). (2010). *AJCC cancer staging manual*. 7th ed. Springer.

Ferlay, J., Soerjomataram, I., Ervik, M., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D., Forman, D., & Bray, F. (n.d.). *GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0. IARC CancerBase No. 11*. Retrieved August 18, 2020, from http://globocan.iarc.fr/

Gripp, S., Haller, J. C., Metz, J., & Willers, R. (2000). Prostate-specific antigen: Effect of pelvic irradiation. *Radiology*, *215*(3), 757–760. https://doi.org/10.1148/radiology.215.3.r00jn09757

Halamkova, J., Kazda, T., Pehalova, L., Gonec, R., Kozakova, S., Bohovicova, L., Krakorova, D. A., Slaby, O., Demlova, R., Svoboda, M., & Kiss, I. (2021). Second primary malignancies in colorectal cancer patients. *Scientific Reports*, *11*(1), 2759. https://doi.org/10.1038/s41598-021-82248-7

Hemminki, K., Santi, I., Weires, M., Thomsen, H., Sundquist, J., & Bermejo, J. L. (2010). Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. *BMC Cancer*, *10*(1), 688. https://doi.org/10.1186/1471-2407-10-688

Herrmann, C., Cerny, T., Savidan, A., Vounatsou, P., Konzelmann, I., Bouchardy, C., Frick, H., & Ess, S. (2013). Cancer survivors in Switzerland: A rapidly growing population to care for. *BMC Cancer*, *13*(1), 287. https://doi.org/10.1186/1471-2407-13-287

Hoffman, K. E., Hong, T. S., Zietman, A. L., & Russell, A. H. (2008). External beam radiation treatment for rectal cancer is associated with a decrease in subsequent prostate cancer diagnosis. *Cancer*, *112*(4), 943–949. https://doi.org/10.1002/cncr.23241

Howe, H. L. (Ed.). (2003). A review of the definition for multiple primary cancers in the United States. In *North American Association of Cancer Registries*. Workshop proceedings from December 4-6, 2002, in Princeton, New Jersey. Springfield (IL).

Iacopetta, B. (2002). Are there two sides to colorectal cancer? *International Journal of Cancer*, *101*(5), 403–408. https://doi.org/10.1002/ijc.10635

Jacobs, C. D., Trotter, J., Palta, M., Moravan, M. J., Wu, Y., Willett, C. G., Lee, W. R., & Czito, B. G. (2020). Multi-institutional analysis of synchronous prostate and Rectosigmoid cancers. *Frontiers in Oncology*, *10*, 345. https://doi.org/10.3389/fonc.2020.00345

Jin, T., Song, T., Deng, S., & Wang, K. (2014). Radiation-induced secondary malignancy in prostate cancer: A systematic review and meta-analysis. *Urologia Internationalis*, *93*(3), 279–288. https://doi.org/10.1159/000356115

Kamiyama, H., Sakamoto, K., China, T., Aoki, J., Niwa, K., Ishiyama, S., Takahashi, M., Kojima, Y., Goto, M., Tomiki, Y., & Horie, S. (2016). Combined laparoscopic abdominoperineal resection and robotic-assisted prostatectomy for synchronous double cancer of the rectum and the prostate. *Asian Journal of Endoscopic Surgery*, *9*(2), 142–145. https://doi.org/10.1111/ases.12265

Kavanagh, D. O., Quinlan, D. M., Armstrong, J. G., Hyland, J. M. P., O'Connell, P. R., & Winter, D. C. (2012). Management of synchronous rectal and prostate cancer. *International Journal of Colorectal Disease*, *27*(11), 1501–1508. https://doi.org/10.1007/s00384-012-1465-z

Lane, Z., Epstein, J. I., Ayub, S., & Netto, G. J. (2008). Prostatic adenocarcinoma in colorectal biopsy: Clinical and pathologic features. *Human Pathology*, *39*(4), 543–549. https://doi.org/10.1016/j.humpath.2007.08.011

las Heras Alonso, M. M., & Gelabert Mas, A. (2010). Independent multiple primary tumors and second primary neoplasms. Relationship between smoking. *Actas Urológicas Españolas (English Edition)*, *34*(6), 516–521. https://doi.org/10.1016/s2173-5786(10)70123-2

Lin, C., Jin, K., Hua, H., Lin, J., Zheng, S., & Teng, L. (2011). Synchronous primary carcinomas of the rectum and prostate: Report of three cases. *Oncology Letters*, *2*(5), 817–819. https://doi.org/10.3892/ol.2011.323

Liu, L., De Vries, E., Louwman, M., Aben, K., Janssen-Heijnen, M., Brink, M., Coebergh, J. W., & Soerjomataram, I. (2011). Prevalence of multiple malignancies in the Netherlands in 2007. *International Journal of Cancer*, *128*(7), 1659–1667. https://doi.org/10.1002/ijc.25480

Liu, Z. H., Li, C., Kang, L., Zhou, Z. Y., Situ, S., & Wang, J. P. (2015). Prostate cancer incorrectly diagnosed as a rectal tumor: A case report. *Oncology Letters*, *9*(6), 2647–2650. https://doi.org/10.3892/ol.2015.3100

Lv, M., Zhang, X., Shen, Y., Wang, F., Yang, J., Wang, B., Chen, Z., Li, P., Zhang, X., Li, S., & Yang, J. (2017). Clinical analysis and prognosis of synchronous and metachronous multiple primary malignant tumors. *Medicine (United States)*, *96*(17), e6799. https://doi.org/10.1097/MD.0000000000006799

McNeal, J. E., Redwine, E. A., Freiha, F. S., & Stamey, T. A. (1988). Zonal distribution of prostatic adenocarcinoma: Correlation with histologic pattern and direction of spread. *American Journal of Surgical Pathology*, *12*(12), 897–906. https://doi.org/10.1097/00000478-198812000-00001

Moore, M., Feakins, R. M., & Lauwers, G. Y. (2020). Non-neoplastic colorectal disease biopsies: Evaluation and differential diagnosis. *Journal of Clinical Pathology 73* (12), 783–792. https://doi.org/10.1136/jclinpath-2020-206794

Mourra, N., Parc, Y., McNamara, D., Tiret, E., Flejou, J. F., & Parc, R. (2005). Lymph node metastases of prostatic adenocarcinoma in the mesorectum in patients with adenocarcinoma or villous tumor of the rectum with collision phenomenon in a single lymph node: Report of five cases. *Diseases of the Colon and Rectum*, *48*(2), 384–389. https://doi.org/10.1007/s10350-004-0776-8

Murray, S. K., Breau, R. H., Guha, A. K., & Gupta, R. (2004). Spread of prostate carcinoma to the perirectal lymph node basin: Analysis of 112 rectal resections over a 10-year span for primary rectal adenocarcinoma. *American Journal of Surgical Pathology*, *28*(9), 1154–1162. https://doi.org/10.1097/01.pas.0000131543.80147.3d

Nash, G. F., Turner, K. J., Hickish, T., Smith, J., Chand, M., & Moran, B. J. (2012). Interactions in the aetiology, presentation and management of synchronous and metachronous adenocarcinoma of the prostate and rectum. *Annals of the Royal College of Surgeons of England*, *94*(7), 456–462. https://doi.org/10.1308/003588412X13373405384611

Nieder, A. M., Porter, M. P., & Soloway, M. S. (2008). Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: A population based cohort study. *Journal of Urology*, *180*(5), 2005–2010. https://doi.org/10.1016/j.juro.2008.07.038

Osunkoya, A. O., Netto, G. J., & Epstein, J. I. (2007). Colorectal adenocarcinoma involving the prostate: report of 9 cases. *Human Pathology*, *38*(12), 1836–1841. https://doi.org/10.1016/j.humpath.2007.04.021

Rapiti, E., Fioretta, G., Verkooijen, H. M., Zanetti, R., Schmidlin, F., Shubert, H., Merglen, A., Miralbell, R., & Bouchardy, C. (2008). Increased risk of colon cancer after external radiation therapy for prostate cancer. *International Journal of Cancer*, *123*(5), 1141–1145. https://doi.org/10.1002/ijc.23601

Rawla, P. (2019). Epidemiology of prostate cancer. *World Journal of Oncology*, *10*(2), 63–89. https://doi.org/10.4021/wjon.v10i2.1191

Rawla, P., Sunkara, T., & Barsouk, A. (2019). Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. *Przeglad Gastroenterologiczny*, *14* (2), 89–103. https://doi.org/10.5114/pg.2018.81072

SEER. (1998). *Program Code Manual*, 3rd ed. National Cancer Institute.

Seretis, C., Seretis, F., & Liakos, N. (2014). Multidisciplinary approach to synchronous prostate and rectal cancer: Current experience and future challenges. *Journal of Clinical Medicine Research*, *6*(3), 157–161. https://doi.org/10.14740/jocmr1796w

Sharp, H. J., Swanson, D. A., Pugh, T. J., Zhang, M., Phan, J., Kudchadker, R., Bruno, T. L., Kuban, D. A., Lee, A. K., Choi, S., Nguyen, Q. N., Hoffman, K. E., McGuire, S. E., & Frank, S. J. (2012). Screening colonoscopy before prostate cancer treatment can detect colorectal cancers in asymptomatic patients and reduce the rate of complications after brachytherapy. *Practical Radiation Oncology*, *2*(3), e7–e13. https://doi.org/10.1016/j.prro.2011.11.010

Sirovich, B. E., Schwartz, L. M., & Woloshin, S. (2003). Screening men for prostate and colorectal cancer in the United States: Does practice reflect the evidence? *Journal of the American Medical Association*, *289*(11), 1414–1420. https://doi.org/10.1001/jama.289.11.1414

Sturludóttir, M., Martling, A., Carlsson, S., & Blomqvist, L. (2015). Synchronous rectal and prostate cancer - The impact of MRI on incidence and imaging findings. *European Journal of Radiology*, *84*(4), 563–567. https://doi.org/10.1016/j.ejrad.2014.12.030

Tang, T., Yang, Z., Zhang, D., Qu, J., Liu, G., & Zhang, S. (2017). Clinicopathological study of 9 cases of prostate cancer involving the rectal wall. *Diagnostic Pathology*, *12*, 8. https://doi.org/10.1186/s13000-017-0599-2

Terris, M. K., & Wren, S. M. (2001). Results of a screening program for prostate cancer in patients scheduled for abdominoperineal resection for colorectal pathologic findings. *Urology*, *57*(5), 943–945. https://doi.org/10.1016/S0090-4295(01)00943-8

Testori, A., Cioffi, U., De Simone, M., Bini, F., Vaghi, A., Lemos, A. A., Ciulla, M. M., & Alloisio, M. (2015). Multiple primary synchronous malignant tumors. *BMC Research Notes*, *8*(1), 1–4. https://doi.org/10.1186/s13104-015-1724-5

Tziris, N., Dokmetzioglou, J., Giannoulis, K., Kesisoglou, I., Sapalidis, K., Kotidis, E., & Gambros, O. (2008). Synchronous and metachronous adenocarcinomas of the large intestine. *Hippokratia*, *12*(3), 150–152.

Vaghefi, H., Magi-Galluzzi, C., & Klein, E. A. (2005). Local recurrence of prostate cancer in rectal submucosa after transrectal needle biopsy and radical prostatectomy. *Urology*, *66*(4), 881.e7-881.e9. https://doi.org/10.1016/j.urology.2005.04.005

Van Hemelrijck, M., Drevin, L., Holmberg, L., Garmo, H., Adolfsson, J., & Stattin, P. (2012). Primary cancers before and after prostate cancer diagnosis. *Cancer*, *118*(24), 6207–6216. https://doi.org/10.1002/cncr.27672

Vogt, A., Schmid, S., Heinimann, K., Frick, H., Herrmann, C., Cerny, T., & Omlin, A. (2017). Multiple primary tumours:

Challenges and approaches, a review. *ESMO Open*, *2*(2), 1–11. https://doi.org/10.1136/esmoopen-2017-000172

Wallis, C. J. D., Mahar, A. L., Choo, R., Herschorn, S., Kodama, R. T., Shah, P. S., Danjoux, C., Narod, S. A., & Nam, R. K. (2016). Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. *BMJ*, *352*, i851. https://doi.org/10.1136/bmj.i851

Warren, S. (1932). Multiple primary malignant tumors. A survey of the literature and a statistical study. *Am J Cancer*, *16*, 1358–1414.

Weir, H. K., Johnson, C. J., & Thompson, T. D. (2013). The effect of multiple primary rules on population-based cancer survival. *Cancer Causes and Control*, *24*(6), 1231–1242. https://doi.org/10.1007/s10552-013-0203-3