ANTICANCER RESEARCH *42*: 4217-4235 (2022)
doi:10.21873/anticanres.15922

Review

Comparison of Proportion of Elevated Carcinoembryonic Antigen Levels in Patients With Appendiceal and Colorectal Adenocarcinoma: A Systematic Review and Meta-analysis

ADAM T. CRISTAUDO[1], SCOTT B. JENNINGS[2] and DAVID L. MORRIS[1]

[1]*Liver & Peritonectomy Unit, Department of Surgery, St George Hospital, Kogarah, NSW, Australia;*
[2]*Department of Cardiothoracic Surgery, Prince of Wales Hospital, Sydney, NSW, Australia*

Abstract. *Background/Aim: The proportion of patients with liver metastases in patients with appendiceal versus colorectal adenocarcinomas was 3.1 percent and 24 percent, respectively, in our peritonectomy centre. From our internal analyses, carcinoembryonic antigen (CEA) was potentially involved. A hypothesis was proposed regarding the natural progression of appendiceal adenocarcinoma. To support this, a systematic review and meta-analysis were performed to examine whether there was a difference in the proportion of patients with an elevated CEA in appendiceal versus colorectal adenocarcinoma patients in the current literature. Materials and Methods: Medline (PubMed), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature, Clinicaltrials.gov, Web of Science, and Google Scholar were searched. All studies involving patients with appendiceal and/or colorectal adenocarcinoma were eligible. Data were analysed by grouping appendiceal and colorectal adenocarcinoma in separate meta-analyses, and then comparing their weighted proportions of elevated CEA. Principal summary measures were weighted proportions of patients with elevated CEA. Results: From the initial identification of 1,928 articles, 136 articles were included in the final synthesis. Ninety-two articles were included in the meta-analysis. Proportions of appendiceal and colorectal adenocarcinoma with elevated CEA were 56% (95%CI=47-65%) and 42% (95%CI=38-46%), respectively (p=0.0001). Conclusion: Patients with appendiceal adenocarcinoma had a higher proportion of CEA than those with colorectal adenocarcinoma. Future studies should focus on the several aspects of CEA presented in patients with appendiceal adenocarcinoma. This could provide treatments for patients with colorectal adenocarcinoma by preventing the development of liver metastases.*

Correspondence to: Adam T. Cristaudo, Department of Surgery, St George Hospital, Pitney Building, Short Street, Kogarah, NSW, 2217, Australia. Tel: +61 291131493, Fax: +61 291131544, e-mail: adamcristaudo@gmail.com

Key Words: Colorectal, appendiceal, peritonectomy, adenocarcinoma, carcinoembryonic antigen, review.

Differences between appendiceal and colorectal adenocarcinoma have been published extensively, with the most recent regarding gene expression between 'high-risk' appendiceal cancer and colorectal cancer (1). Mucin 2 and 5AC, and trefoil factors 1 and 2 are just a few of the many and different genes expressed in the 'high-risk' appendiceal cancer patients; whereas homeobox A9 and trinucleotide repeat containing 9 genes are more predominantly expressed in patients with colorectal cancer. The roles of these genes and how they make appendiceal cancer different from colorectal cancer are thought-provoking.

There was a significant difference in the proportion of liver metastases between appendiceal and colorectal adenocarcinomas in our peritonectomy unit, 3.1 percent (n=9/289) and 24 percent (n=95/395, p=0.0001). The reasons behind this have been explored internally. Our results pointed to carcinoembryonic antigen (CEA), a commonly used tumour marker, being potentially involved. CEA is a glycoprotein that belongs to the supergene family of immunoglobulins. The serum level of CEA is used clinically for diagnosis and recurrence surveillance, particularly in patients with colorectal cancer.

A recent paper by Lee and Lee (2) described the role of CEA in the development of liver metastases in patients with colorectal cancer. CEA released by colon cancer cells travels through the portal vein and interacts with a membrane-anchored

Table I. *Search terms used in systematic review.*

Medical subject headings (MeSH)	Not used
Free text words	Append* adenocarcinoma
	Append* AND carcinoembryonic antigen
	Colorectal adenocarcinoma AND carcinoembryonic antigen
	Colorectal cancer AND carcinoembryonic antigen
	Colorectal adenocarcinoma
	Pseudomyxoma peritonei AND carcinoembryonic antigen
	PMP AND carcinoembryonic antigen
Field	All fields
Limits	None

homolog of heterogeneous nuclear protein M4 (hnRNP M4) on hepatic Kupffer cells (either cytoplasmatic or membranous). This interaction creates a pro-metastatic cascade, which can lead to the development of liver metastases in patients with colorectal cancer (where CEA is positively expressed).

Objectives. A hypothesis has been proposed regarding the natural progression of appendiceal adenocarcinoma (3). To support this, we performed a systematic review and meta-analysis to examine whether there is evidence that the proportion of patients with appendiceal cancer that have an elevated CEA differs from that in patients with colorectal adenocarcinoma.

Materials and Methods

In accordance with the PRISMA guidelines, the systematic review was conducted and reported (4). The protocol has been registered with PROSPERO (CRD42021283615) and is available online (5).

Eligibility criteria. All studies that included hospitalised patients with appendiceal and colorectal adenocarcinoma, aged 18 years or older, were eligible for inclusion. All published and unpublished studies were considered. Reviews, editorials, case reports, paediatric case series, and non-peer-reviewed articles were excluded.

Information sources. Using the following electronic databases: Medline (PubMed), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, Clinicaltrials.gov, Web of Science, and Google Scholar, a systematic literature search was conducted. Dates of publication were not restricted, with dates of coverage including from January 1950, up until a final search performed on the 26th of September, 2021. Additional relevant articles were manually scanned through the reference lists of all included studies and relevant review papers. By letter or e-mail, the corresponding authors were also requested to provide unpublished data from relevant trials.

Search strategy. The search strategy was constructed in consultation with a senior staff librarian (Table I). Authors (A Cristaudo and S Jennings) independently searched the above databases using keywords related to appendiceal and colorectal adenocarcinoma and carcinoembryonic antigen. A manual search for electronic links to relevant articles and references to selected articles was also performed. No restrictions were placed regarding language, however, only those in English or translated from Turkish, Chinese, Bulgarian, Polish, and Japanese were included in this systematic review.

Selection process. All studies that included patients with either appendiceal or colorectal adenocarcinoma in patients 18 years and above that mentioned CEA were eligible for inclusion from the systematic review literature search. Screening, eligibility, inclusion in the systematic review, and subsequent meta-analysis of studies were performed as per the PRISMA statement by two authors independently (A Cristaudo and S Jennings) (4). Titles, followed by abstracts, and then full-text articles were retrieved and read by both authors to identify those to be included in the systematic review. Data extraction disagreements between two authors were primarily resolved by discussion and consensus. A consensus meeting with a third author (D Morris) resolved disagreements if this failed.

Data collection process. Data were collected independently as per the PRISMA statement by two authors (A Cristaudo and S Jennings) using an electronic database (4). To confirm unclear data and to obtain additional data not available in the original article, investigators of included studies were contacted.

Data items. The collected data included study characteristics (first author's surname, publication year, and study design), patient characteristics (number of patients, mean or median age), overall cancer type, the type/stage/grade of the primary tumour, CEA cut-off value (including units of measure), and the number and proportion of patients with elevated CEA. Missing data were handled as follows: Firstly, if the proportion of patients with an elevated CEA was not mentioned in the article, it was calculated by dividing the number of patients with an elevated CEA by the total number of patients who had their CEA measured. Secondly, if the CEA cut-off value was not specified, the study was excluded from the subsequent meta-analysis, even if the proportion of patients with an elevated CEA was still available. Lastly, if the outcome of interest was not available, it was not described, and hence the study (and patients) was excluded from the subsequent meta-analysis. No imputation methods were used.

Study risk of bias assessment. A methodological quality assessment was performed for included studies using the Newcastle-Ottawa quality assessment scale (6).

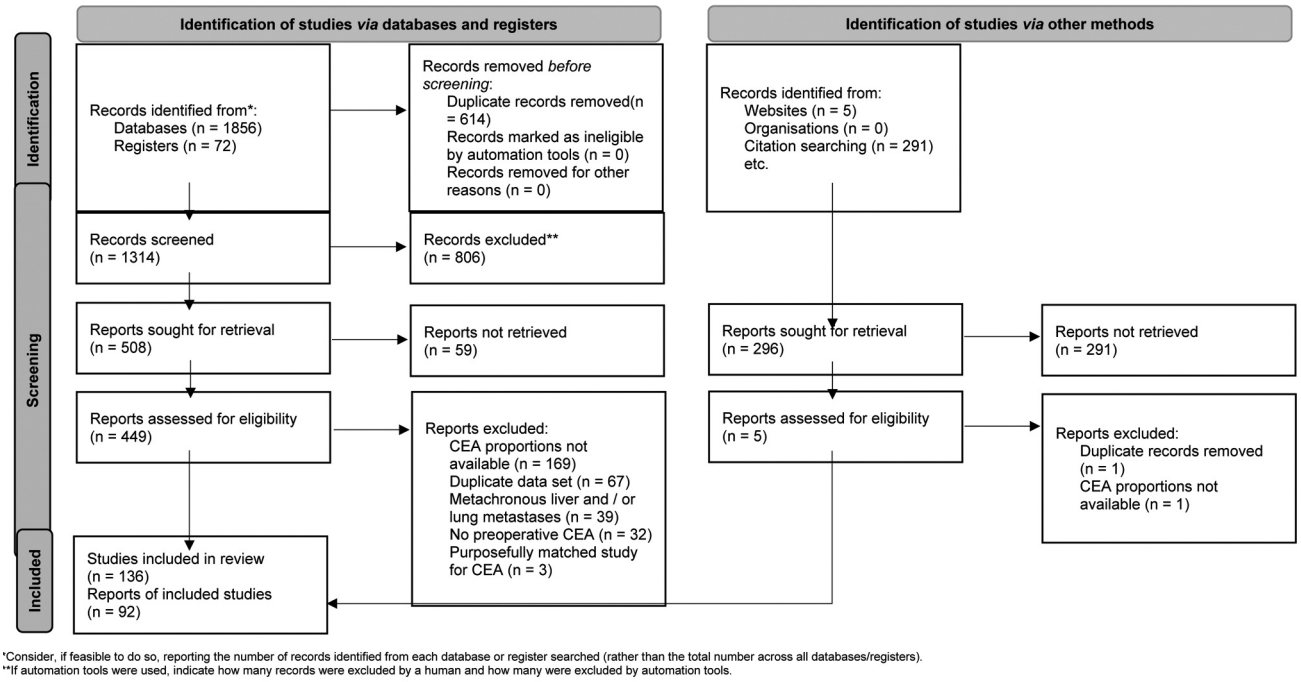

Figure 1. *PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources (148).*

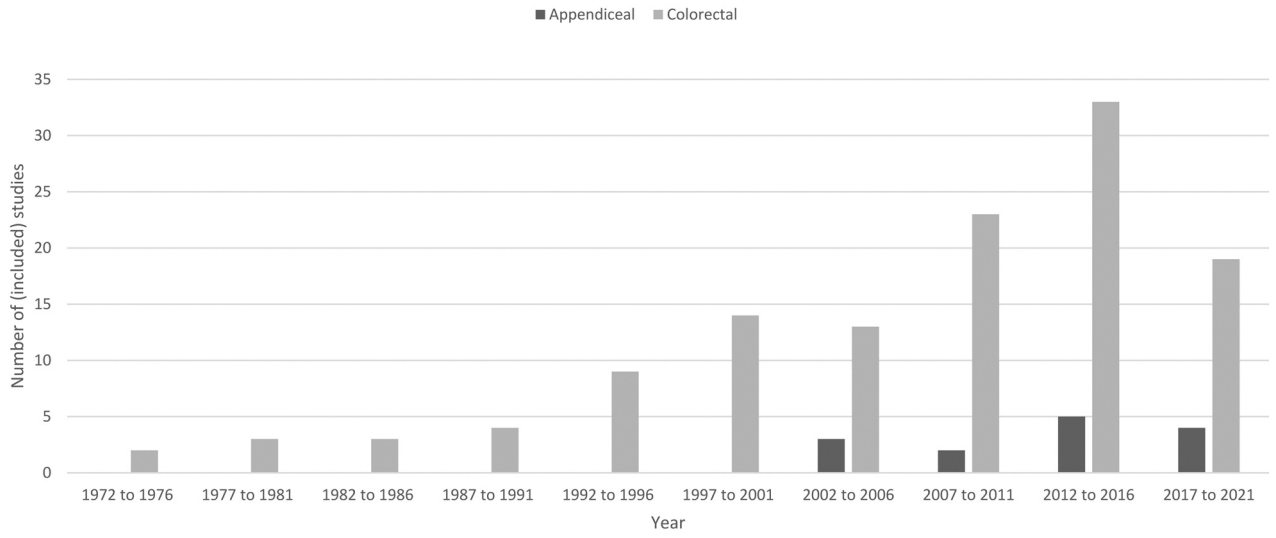

Figure 2. *Number of publications for appendiceal versus colorectal adenocarcinoma from 1972 to 2021.*

Effect measures. An assessment of the proportion of patients with elevated CEA was the primary key summary measure used in the synthesis of data. Appendiceal and colorectal adenocarcinoma proportions were weighted separately using a meta-analysis.

Synthesis methods. Data collected were qualitatively synthesised noting the number of studies for appendiceal and colorectal adenocarcinoma, as well as the proportion of elevated CEA reported in each study. Data were then quantitatively analysed for appendiceal and colorectal adenocarcinoma using MedCalc® Statistical Software version 20.022. to calculate the overall weighted proportion based on a meta-analysis of proportions (7). An evaluation of heterogeneity was conducted using I2 statistics.

Reporting bias assessment. Egger and Begg's tests were used to evaluate the risk of publication bias. The Egger's test estimates the

Table II. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Alexander-Sefre *et al.* (15)	2005	Prospective, cohort	53 (IQR: N/A)	LAMN	5 ng/ml	32	44	14	4
Aziz *et al.* (18)	2018	Retrospective, case-control	54 (IQR: N/A)	Appendiceal Adenocarcinoma	5 ng/ml	61	16	10	6
Baratti *et al.* (22)	2007	Prospective, cohort	56 (IQR: N/A)	LAMN/HAMN	5 ng/ml	62	73	45	6
Canbay *et al.* (25)	2013	Retrospective, case-control	55 (SD: 15)	LAMN/HAMN	5 ng/ml	448	73	327	5
Carmignani *et al.* (27)	2004	Prospective, cohort	N/A	Appendiceal Adenocarcinoma	5 ng/ml	532	56	298	6
Chua *et al.* (37)	2012	Prospective, cohort	53 (IQR: N/A)	LAMN	5 ng/ml	102	65	66	6
Di Fabio *et al.* (39)	2016	Retrospective, case-control	55 (IQR: 46-65)	LAMN/HAMN	5 μg/l	747	45	338	5
Fackche *et al.* (44)	2021	Retrospective, cohort	55 (SD: 12)	Appendiceal Adenocarcinoma	3 ng/ml	383	63	242	5
Järvinen *et al.* (68)	2013	Prospective, cohort	57 (SD: 1.2)	LAMN/HAMN	5 μg/l	89	46	41	5
Ma *et al.* (86)	2020	Retrospective, cohort	53 (IQR: N/A)	Appendiceal Adenocarcinoma	Not stated	50	66	33	5
Nummela *et al.* (96)	2016	Retrospective, cohort	N/A	LAMN/HAMN	5 μg/l	91	56	51	5
van Eden *et al.* (128)	2019	Prospective, cohort	N/A	LAMN/HAMN	5 μg/l	189	65	123	5
van Ruth *et al.* (129)	2002	Retrospective, cohort	58 (IQR: N/A)	LAMN/HAMN	5 μg/l	63	75	47	5
Wagner *et al.* (130)	2013	Prospective, cohort	54 (SD: N/A)	Appendiceal Adenocarcinoma	5 ng/ml	176	54	95	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 μg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; LAMN: low-grade appendiceal mucinous neoplasm; HAMN: high-grade appendiceal mucinous neoplasm.

Table III. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
A Joint *et al.* (63)	1972	Prospective, cohort	N/A	CRC Dukes' A to C	5 ng/ml	115	43	49	4
Abe *et al.* (8)	2016	Retrospective, cohort	N/A	CRC Stage IV	5 ng/ml	129	74	95	5
Adachi *et al.* (9)	1994	Retrospective, cohort	68 (SD: N/A)	Right-sided colon cancer only	3 ng/ml	57	47	27	4
Adrover *et al.* (10)	1999	Retrospective, cohort	66 (SD: N/A)	CRC Stage IV	5 ng/ml	100	58	58	5
Ahmed *et al.* (11)	2018	Prospective, cohort	70(IQR: 60-78)	Metastatic CRC	5 μg/l	1,947	86	1,667	6
Akbulut *et al.* (12)	2002	Prospective, cohort	53 (IQR: N/A)	CRC Stage I to IV	10 ng/ml	52	64	33	5
Aldulaymi *et al.* (14)	2010	Prospective, cohort	65 (IQR: N/A)	LARC – Excluded distant metastases	5 μg/l	33	30	10	5
Alici *et al.* (16)	2003	Retrospective, cohort	55 (IQR: N/A)	Non-metastatic CRC Stage II and III	3.5 ng/ml	466	39	183	5
Al-Sarraf *et al.* (13)	1979	Retrospective, cohort	N/A	Advanced CRC	5 ng/ml	107	71	76	3
Ayude *et al.* (17)	2003	Retrospective, cohort	68 (SD: N/A)	CRC Dukes' A to D	5 ng/ml	89	25	22	4
Bai *et al.* (19)	2018	Retrospective, cohort	65 (SD: N/A)	CRC Stage I to IV	4.6 μg/ml	1,012	41	415	4
Bao *et al.* (20)	2016	Retrospective, cohort	59 (SD: 13)	Colon Cancer Stage III – Excluded Rectal	5 ng/ml	184	31	57	4
Baqar *et al.* (21)	2019	Retrospective, cohort	73 (IQR: N/A)	CRC Stage III	2.5 ng/ml	532	52	278	4
Bhatavdekar *et al.* (23)	2001	Retrospective, case-control	N/A	CRC Dukes' B and C	5 ng/ml	98	56	55	6
Boey *et al.* (24)	1984	Prospective, cohort	64 (IQR: N/A)	CRC Stage I to III	5 ng/ml	51	63	32	4

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer.

Table IV. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Cardoso *et al*. (26)	2009	Retrospective, cohort	62 (SD: 13)	CRC Stage I to IV	5 ng/ml	154	40	62	3
Carpelan-Holmström *et al*. (28)	2004	Retrospective, cohort	68 (SD: N/A)	CRC Dukes' A to D	5 μg/l	102	35	36	6
Carriquiry *et al*. (29)	1999	Retrospective, cohort	67 (SD: N/A)	CRC Stage I to IV	5 ng/ml	83	40	33	6
Carvalho *et al*. (30)	2017	Prospective, cohort	N/A	CRC Stage I to IV	5 ng/ml	50	46	23	6
Chan *et al*. (31)	2010	Retrospective, case-control	64 (SD: N/A)	CRC Dukes' A to D	5 ng/ml	94	43	40	6
Chang *et al*. (32)	2012	Retrospective, case-control	34 (SD: N/A)	CRC Stage I to IV	5 μg/l	15	20	3	8
Chen *et al*. (33)	2015	Retrospective, case-control	N/A	CRC Stage I to IV	5 μg/l	1,250	42	529	5
Chiang *et al*. (34)	2012	Retrospective, cohort	63 (SD: N/A)	CRC Stage I to III	5 ng/ml	3,830	33	1,275	7
Cho *et al*. (35)	2011	Prospective, cohort	64 (IQR: N/A)	CRC Stage I to IV	Not stated	402	20	81	6
Choi *et al*. (36)	2012	Prospective, cohort	63 (IQR: N/A)	CRC Stage I to IV	Not stated	397	20	78	6
Cunningham *et al*. (38)	1986	Retrospective, cohort	N/A	CRC Dukes' A to D	2.5 ng/ml	26	73	19	4
Diez *et al*. (40)	2000	Retrospective, cohort	67 (SD: N/A)	CRC Stage I to III	5 ng/ml	174	35	60	5
Dirican *et al*. (41)	2014	Prospective, cohort	59 (IQR: N/A)	Metastatic CRC	10 ng/ml	45	54	24	5
Dragutinović *et al*. (42)	2011	Retrospective, case-control	N/A	CRC Stage I to IV	5 ng/ml	30	43	13	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma).

Table V. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Du *et al*. (43)	2013	Retrospective, cohort	56 (IQR: N/A)	LARC – Stage I to IIIC	5 ng/ml	303	34	102	4
Forones *et al*. (45)	1997	Retrospective, cohort	N/A	CRC Dukes' A to D	5 ng/ml	109	42	46	3
Frikart *et al*. (46)	1995	Prospective, cohort	59 (SD: N/A)	CRC with or without Liver Metastases	5 ng/ml	41	51	21	5
Fu *et al*. (47)	2020	Retrospective, cohort	59 (IQR: 50-67)	CRC Stage I to III	5 ng/ml	530	32	169	6
Gago *et al*. (48)	2020	Retrospective, cohort	64 (SD: 10)	Rectal Cancer Stage II or III	5 ng/ml	81	42	34	4
Gao *et al*. (49)	2014	Retrospective, cohort	62 (SD: 13)	Rectal Cancer Stage I to IV	5 ng/ml	392	55	214	7
Gasser *et al*. (50)	2007	Retrospective, cohort	66 (SD: 5.4)	CRC Stage I to III – Excluded Stage IV	5 ng/ml	492	31	154	5
Germa-Lluch *et al*. (51)	1991	Prospective, cohort	N/A	CRC Dukes' A to D	2.5 ng/ml	21	38	8	5
Goslin *et al*. (52)	1981	Retrospective, case-control	N/A	CRC Dukes' A to D	2.5 ng/ml	17	41	7	6
Guadagni *et al*. (53)	1993	Retrospective, case-control	64 (SD: 1.3)	CRC Dukes' A to D	5 ng/ml	200	43	86	7
Gunawardene *et al*. (54)	2018	Retrospective, cohort	71 (IQR: N/A)	CRC Stage I to IV	3.3 ng/ml	138	53	73	7
Hamada *et al*. (55)	1985	Retrospective, cohort	59 (SD: N/A)	CRC Dukes' A to D	10 ng/ml	60	62	37	4
Han *et al*. (56)	2014	Retrospective, case-control	62 (SD: N/A)	CRC Dukes' A to D	3.4 ng/ml	95	54	51	7
Hotta *et al*. (57)	2006	Prospective, cohort	65 (IQR: N/A)	CRC Stage IV with Liver Metastases	1 ng/ml	23	70	16	4
Huang *et al*. (59)	2021	Retrospective, cohort	58 (SD: 15)	Mucinous CRC Stage I to III	5 ng/ml	162	47	76	4

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer.

Table VI. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Huang *et al.* (58)	2014	Retrospective, cohort	64 (IQR: N/A)	Rectal Cancer Stage I to III – Excluded Stage IV	5 ng/ml	284	38	108	5
Hung *et al.* (60)	2017	Retrospective, cohort	65 (SD: N/A)	CRC Stage I to IV	5 ng/ml	10,800	42	4,547	4
Huo *et al.* (61)	2016	Prospective, cohort	55 (SD: N/A)	CRPC	6.5 mg/l	163	50	81	7
Iarŭmov *et al.* (62)	1998	Retrospective, cohort	N/A	CRC with or without Liver Metastases	2.5 ng/ml	86	49	42	5
Ishiguro *et al.* (64)	2009	Retrospective, cohort	55 (IQR: N/A)	LARC – T4 only	10 ng/ml	93	37	34	4
Ishizuka *et al.* (65)	2001	Retrospective, cohort	59 (SD: N/A)	CRC with Liver Metastases	5 ng/ml	73	81	59	4
Ishizuka *et al.* (66)	2010	Retrospective, cohort	N/A	CRC Stage I, III, and IV	6 ng/ml	145	12	17	4
Jang *et al.* (67)	2012	Retrospective, cohort	N/A	CRC Stage I to IV	5 ng/ml	220	31	68	4
Jensen *et al.* (69)	2008	Retrospective, cohort	71 (IQR: 61-79)	CRC Stage I to IV	5 ng/ml	130	19	24	4
Jones *et al.* (70)	2013	Retrospective, case-control	N/A	CRC with Liver Metastases	5 ng/ml	95	60	57	6
Jubert *et al.* (71)	1978	Retrospective, cohort	65 (SD: N/A)	CRC Dukes' A to D	2.5 ng/ml	97	58	56	3
Kang *et al.* (72)	2010	Prospective, cohort	59 (IQR: N/A)	CRC Stage II and III	5 ng/ml	285	37	106	5
Khan *et al.* (73)	2020	Retrospective, cohort	N/A	CRC Stage I to III	5 ng/ml	55	76	42	5
Kim *et al.* (75)	2015	Prospective, cohort	64 (IQR: N/A)	CRC Stage I to IV	5 ng/ml	831	17	145	6
Kim *et al.* (74)	2013	Retrospective, cohort	62 (SD: 11)	CRC Stage IIA	6 ng/ml	1,543	18	282	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer; CRPC: Colorectal peritoneal carcinomatosis.

Table VII. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Kuo *et al.* (76)	2011	Prospective, cohort	N/A	CRC Stage I to IV	5 ng/ml	59	37	22	4
Kwon *et al.* (78)	2010	Retrospective, cohort	60 (IQR: 49-71)	CRC Stage III	5 ng/ml	148	40	59	5
Kwon *et al.* (77)	2012	Retrospective, cohort	64 (IQR: 52-76)	CRC Stage I to IV	5 ng/ml	200	22	44	5
Lee *et al.* (79)	2015	Retrospective, cohort	58 (SD: 11)	LARC – Excluded Distant Metastases	5 ng/ml	947	35	331	5
Leu *et al.* (80)	1992	Retrospective, case-control	N/A	CRC Dukes' A to D	3 ng/ml	27	70	19	7
Li *et al.* (81)	2020	Prospective, cohort	N/A	CRC Stage I to IV	5 ng/ml	13,755	22	2,997	5
Liang *et al.* (82)	2002	Prospective, cohort	N/A	CRC Stage IV	3.5 ng/ml	144	89	128	8
Liu *et al.* (83)	2015	Retrospective, cohort	56 (IQR: N/A)	LARC	Not stated	386	5	20	5
Liu *et al.* (84)	2016	Retrospective, cohort	61 (IQR: N/A)	Rectal Cancer with or without Distant Metastases	10 ng/ml	271	25	68	6
Livingstone *et al.* (85)	1974	Prospective, cohort	N/A	CRC Dukes' A to D	2.5 mg/ml	137	65	89	4
Machida *et al.* (87)	2008	Retrospective, cohort	62(IQR: N/A)	Metastatic CRC	5 ng/ml	103	85	87	5
Meling *et al.* (88)	1992	Prospective, cohort	N/A	CRC Dukes' A to D	5 microg/l	363	42	151	4
Melli *et al.* (89)	2021	Retrospective, cohort	68 (SD: 12)	CRC Stage I to IV	5 ng/ml	294	15	43	5
Miyake *et al.* (90)	2019	Retrospective, cohort	64 (IQR: N/A)	CRPC	5 ng/ml	33	52	17	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer; CRPC: Colorectal peritoneal carcinomatosis.

Table VIII. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Morita *et al*. (91)	2004	Retrospective, cohort	63 (SD: 10)	CRC Stage I to IV	5 ng/ml	117	45	53	5
Myerson *et al*. (92)	1995	Retrospective, cohort	63 (SD: N/A)	Rectal – Pre-op RTx – Astler Coller A to C	5 ng/ml	220	29	64	5
Nakagoe *et al*. (93)	2001	Retrospective, cohort	65 (IQR: N/A)	CRC Stage I to IV – without Liver Metastases	2.5 ng/ml	308	43	133	4
Nakamura *et al*. (94)	2020	Retrospective, cohort	62 (IQR: 54-69)	Rectal Cancer Stage I to III	5 ng/ml	1,616	25	408	5
Nozoe *et al*. (95)	2008	Retrospective, cohort	69 (SD: 11)	CRC Dukes' A to D	Not stated	102	39	40	6
Oñate-Ocaña *et al*. (97)	2004	Retrospective, cohort	56 (SD: 15)	CRC Stage I to II	3 ng/ml	124	59	73	5
Ooi *et al*. (98)	2001	Retrospective, cohort	55(SD: N/A)	CRC Dukes' C and D	5 μg/l	9	11	1	6
Painbeni *et al*. (99)	1997	Retrospective, cohort	59 (SD: 9.2)	Metastatic CRC	5 ng/ml	41	73	30	4
Park *et al*. (100)	2015	Retrospective, cohort	60 (IQR: N/A)	Mucinous *vs*. Non-Mucinous CRC Stage I to III	5 ng/ml	6,475	18	1,186	6
Pedrazzani *et al*. (101)	2019	Retrospective, cohort	N/A	CRC with Liver Metastases	200 ng/ml	125	24	30	5
Peng *et al*. (102)	2016	Retrospective, cohort	55 (IQR: N/A)	Rectal Cancer pCRT Stage 0 to IV	2 ng/ml	501	63	315	4
Petrelli *et al*. (103)	1992	Prospective, cohort	63 (IQR: N/A)	CRC Dukes' A to D	5 ng/ml	355	21	75	5
Plebani *et al*. (104)	1996	Retrospective, cohort	N/A	CRC Stage I to IV	5 μg/l	114	37	42	5
Quah *et al*. (105)	2008	Retrospective, cohort	72 (IQR: 65-80)	Metastatic CRC	5 ng/ml	448	27	119	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer; RTx: Radiotherapy; pCRT: pre-operative chemoradiotherapy.

relationship between standard error and the standardised effect using linear regression. Begg's test measures if the rank of effect estimates is significantly correlated with the rank of their variances.

Results

Study selection. The initial database and registry search identified 1,928 studies (Figure 1). This included 1,066 studies from PubMed.gov, 484 studies from Cumulative Index to Nursing and Allied Health Literature, 294 studies from OVID *via* Medline, 72 studies from the clinicaltrials.gov website, and 12 studies from Cochrane Central Register of Controlled Trials. An additional 296 studies were identified from the reference lists of included studies and the Web of Science and Google Scholar websites. Of these, 614 were identified as duplicate studies and subsequently excluded. Systematic exclusions were then made, leaving a total of 136 studies in the final review. The final stage of the systematic review (full text) excluded 312 studies. This was due to studies with no CEA proportions available (169 studies), with duplicate datasets (66 studies), with metachronous liver and/or lung metastases (39 studies), with no pre-operative CEA (32 studies), or where the groups were purposefully matched for CEA (three studies). Forty-four studies were further excluded due to the studies involving low-grade appendiceal mucinous neoplasms (LAMN) alone and/or having cut-off values for CEA that were not 5 ng/ml or 5 μg/l, leaving a total of 92 studies in the subsequent meta-analysis.

Study characteristics and results of individual studies. The 136 included studies involved a total of 67,113 patients, with a mean age of 54.7 [standard deviation (SD): 1.71] years for appendiceal and a mean age of 62.3 (SD=5.59) years for colorectal adenocarcinoma [mean difference (MD)=7.6 years, t(96)=-4.4, p=0.00002] (Figure 2) (8-143). Of the included studies, 122 studies involved 64,088 patients with colorectal adenocarcinoma (published from 1972 to 2021), and 14 studies involved 3,025 patients with appendiceal adenocarcinoma (published from 2002 to 2021). Of the 122 studies involving patients with colorectal adenocarcinoma, 85 studies included patients with metastatic disease (eight studies specifically with liver metastases) and 17 studies included rectal adenocarcinoma only. Of the 14 studies involving patients with appendiceal adenocarcinoma, seven studies included those with either LAMN or high-grade appendiceal neoplasms, five studies included those with adenocarcinoma, and two studies included those with LAMN alone.

Table IX. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Ratto *et al.* (106)	1998	Retrospective, cohort	N/A	CRC Astler Coller Class A to D	5 ng/ml	853	52	445	5
Rosati *et al.* (107)	2002	Prospective, cohort	66 (IQR: N/A)	Metastatic CRC	Not stated	35	69	24	6
Roselli *et al.* (108)	2003	Retrospective, case-control	59 (SD: 9.8)	CRC Dukes' A to D	5 ng/ml	194	29	56	6
Sastre *et al.* (109)	2008	Prospective, case-control	N/A	CRC Stage I to IV	5 ng/ml	89	62	55	6
Schneider *et al.* (110)	1997	Prospective, cohort	N/A	CRC Dukes' A to D	5 ng/ml	231	44	101	6
Selcukbiricik *et al.* (111)	2013	Retrospective, cohort	59 (IQR: N/A)	Metastatic CRC	5 ng/ml	215	50	108	5
Seo *et al.* (112)	1997	Retrospective, cohort	68 (SD: N/A)	CRC Dukes' A to D	5 ng/ml	46	46	21	4
Shen *et al.* (113)	2016	Retrospective, cohort	57 (IQR: 45-66)	CRC Stage I to IV	5 ng/ml	125	39	49	6
Shida *et al.* (114)	2016	Retrospective, cohort	N/A	CRC Stage IV ('unresectable')	30 ng/ml	770	55	425	5
Shiue *et al.* (115)	1989	Retrospective, case-control	N/A	CRC Duke's A to D	5 ng/ml	37	49	18	4
Sisik *et al.* (116)	2013	Prospective, cohort	63 (SD: N/A)	CRC Stage I to IV	5 ng/ml	114	42	48	4
Sohn *et al.* (117)	2017	Retrospective, cohort	60 (SD: 11)	Rectal Cancer pCRT – No Distant Metastases	5 ng/ml	423	35	148	4
Suwanagool *et al.* (118)	1990	Retrospective, cohort	N/A	CRC Dukes' A to C	5 ng/ml	55	64	35	4
Tabuchi *et al.* (119)	1988	Prospective, cohort	N/A	CRC Dukes' A to D	5 ng/ml	83	29	24	4

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); pCRT: pre-operative chemoradiotherapy.

CEA cut-off values used within the included studies ranged from 2 ng/ml to 200 ng/ml. The most common value was 5 ng/ml (μg/l), noted in 71% of the included studies (n=97).

Ninety-four studies had a retrospective design, and 42 studies had a prospective design. Ninety-one studies were cohort studies, while 13 studies were case-control studies. None of the included studies were randomised-controlled trials.

Further study characteristics and outcomes of individual studies are shown in Table II, Table III, Table IV, Table V, Table VI, Table VII, Table VIII, Table IX, Table X and Table XI. Forest plots for included studies for appendiceal and colorectal adenocarcinoma from meta-analyses are shown in Figure 3 and Figure 4.

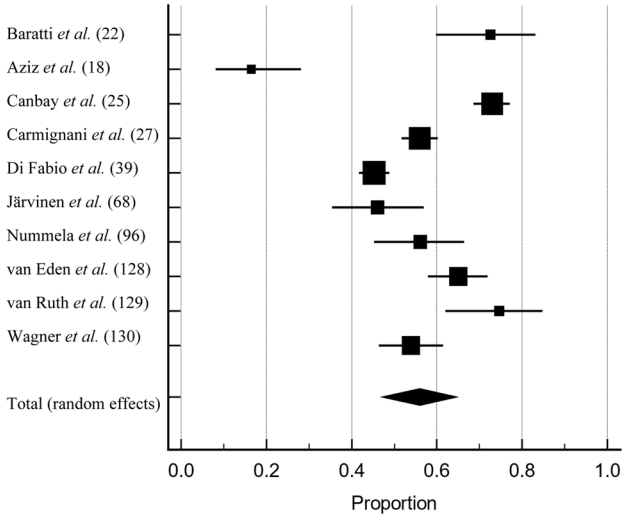

Figure 3. *Forest plot for included studies for appendiceal adenocarcinoma from the meta-analysis.*

Risk of bias in studies. The median score for methodological quality was 5 (IQR=5 to 6), of a possible 9 using the Newcastle-Ottawa quality assessment scale for those included studies that were appendiceal in origin. One study scored 4 points, nine studies scored 5 points, and four studies scored 6 points. For those included studies involving colorectal adenocarcinoma, the median score for methodological quality was 5 (IQR=4 to 6). Four studies scored 3 points, 35 studies scored 4 points, 46 studies scored 5 points, 26 studies scored 6 points, 9 studies scored 7 points, and two studies scored 8 points (out of a possible 9).

Table X. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Takagawa *et al*. (120)	2008	Retrospective, cohort	64 (IQR: 57-71)	CRC Stage I to III	5 ng/ml	638	25	157	5
Takakura *et al*. (121)	2014	Retrospective, cohort	69 (IQR: N/A)	CRPC	5 ng/ml	92	38	35	5
Takeda *et al*. (122)	2007	Retrospective, case-control	64 (SD: N/A)	CRC Stage I to IV	4 ng/ml	182	40	73	4
Tan *et al*. (123)	2010	Retrospective, cohort	53 (IQR: 47-63)	CRC with Krukenberg Tumours	5 ng/ml	21	86	18	6
Thirunavukarasu *et al*. (124)	2010	Retrospective, cohort	69 (SD: 13)	Medullary CRC	Non-/Smoker: 2.5/5 ng/ml	25	40	10	4
Toiyama *et al*. (125)	2008	Prospective, case-control	65 (SD: 11)	CRC Stage I to IV	6 ng/ml	138	41	57	7
Tsai *et al*. (126)	2006	Prospective, cohort	68 (SD: N/A)	CRC Stage IV	5 ng/ml	273	43	116	5
Uejima *et al*. (127)	2021	Retrospective, cohort	71 (SD: 9.9)	CRC Stage II	4.55 ng/ml	135	39	52	5
Waisberg *et al*. (131)	2004	Prospective, cohort	66 (SD: 11)	CRC Dukes' A to C	5 ng/ml	28	29	8	4
Wang *et al*. (133)	2000	Retrospective, cohort	N/A	CRC Dukes' A to C – Dukes' D excluded	5 ng/ml	218	47	103	4
Wang *et al*. (132)	2014	Retrospective, cohort	58 (IQR: N/A)	LARC	5 ng/ml	240	38	90	6
Webb *et al*. (134)	1995	Prospective, cohort	N/A	Advanced CRC	5 ng/ml	342	83	284	5
Weihrauch *et al*. (135)	2002	Prospective, case-control	66 (IQR: N/A)	CRC Stage I to IV	5 ng/ml	51	26	13	6
Yang *et al*. (136)	2016	Retrospective, cohort	64 (SD: N/A)	CRC with Liver Metastases	200 ng/ml	70	34	24	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer; CRPC: Colorectal peritoneal carcinomatosis.

Table XI. *Summarised characteristics and outcomes of the 136 included studies.*

Study name	Study year	Study design	Age*	Type/Stage/ Grade of primary tumour	CEA cut-off value	No. of patients	Proportion (%) CEA (+)	No. with CEA (+)	QAS
Yang *et al*. (137)	2010	Prospective, cohort	N/A	CRC Stage I to IV	5 ng/ml	93	43	40	6
Ye *et al*. (138)	2017	Prospective, cohort	62 (SD: 15)	CRC Dukes' A to D	5 ng/ml	106	32	34	5
Yeo *et al*. (139)	2013	Retrospective, cohort	57 (SD: 11)	LARC Stage II to III	5 ng/ml	609	33	201	5
Yu *et al*. (140)	2013	Prospective, cohort	64 (SD: 1.2)	CRC Stage 0 to IV	5 ng/ml	333	41	137	6
Zhan *et al*. (141)	2013	Prospective, case-control	56 (SD: 10)	Rectal Cancer – Excluded Stage IV	Not stated	221	39	87	7
Zhang *et al*. (142)	2015	Retrospective, cohort	N/A	Rectal Cancer – T3N0M0 only	5 μg/l	270	41	111	5
Zhang *et al*. (143)	2010	Retrospective, cohort	58 (SD: N/A)	CRC with synchronous Liver Metastases	10 ng/ml	160	64	103	5

n: Number of patients; *age either reported as mean with standard deviation or median with inter-quartile range, in years, where applicable; CEA: carcinoembryonic antigen (cut-offs are expressed in units as per individual study – NB: only those with a cut-off value of 5 ng/ml or 5 microg/l are included in the meta-analysis); (+): positive; QAS: Newcastle-Ottawa scale quality assessment score (out of 9); N/A: not available; CRC: colon and rectal cancer (adenocarcinoma); LARC: locally advanced rectal cancer.

Case-control studies specifically report on control selection, comparability of cases and controls based on design or analysis, exposure assessment, and the same assessment methods for cases and controls. In cohort studies, exposure assessments, demonstration of the absence of endpoints of interest at baseline, and endpoint assessments were reported most frequently. The selection of the unexposed cohort or control group and the

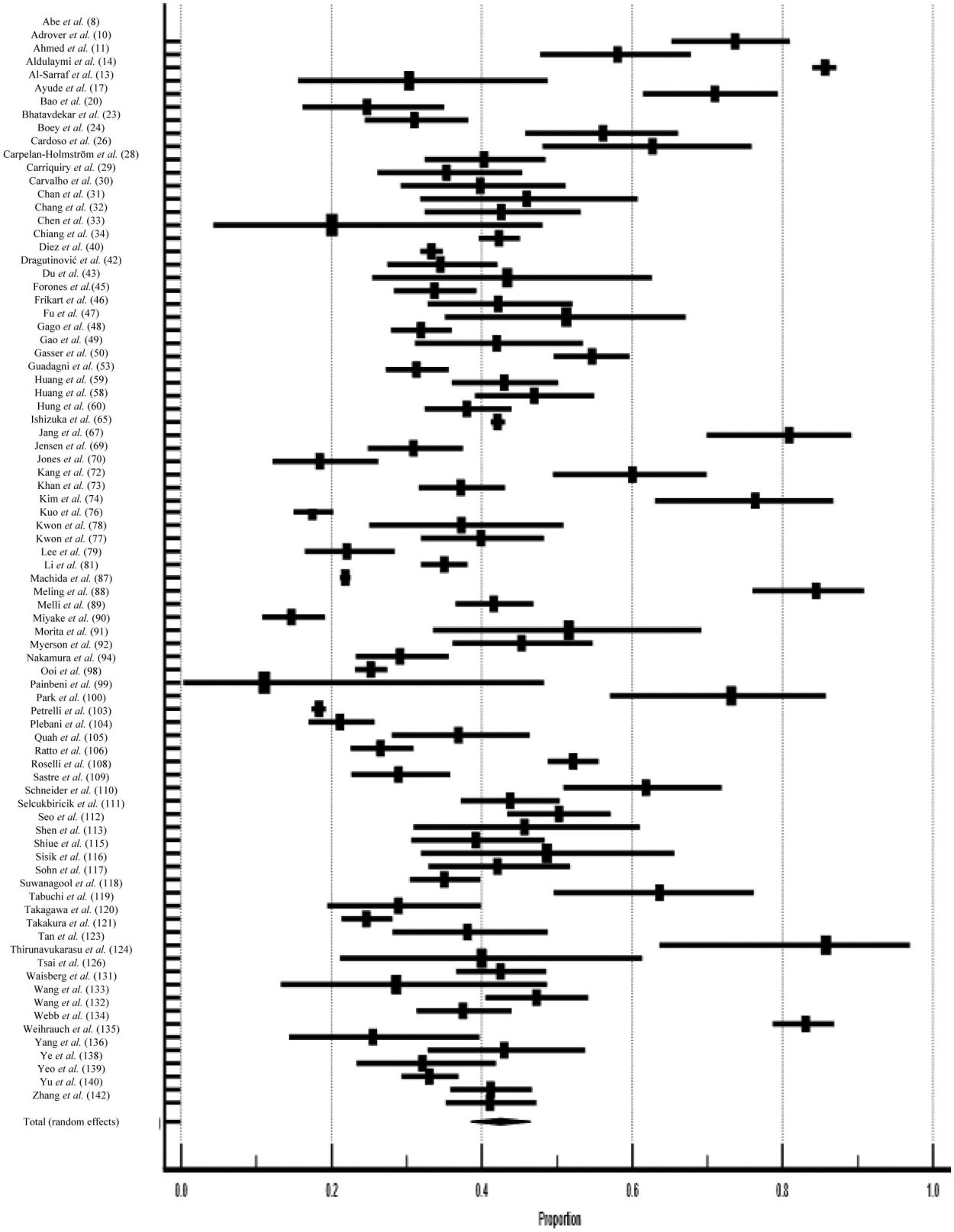

Figure 4. *Forest plot for included studies for colorectal adenocarcinoma from the meta-analysis.*

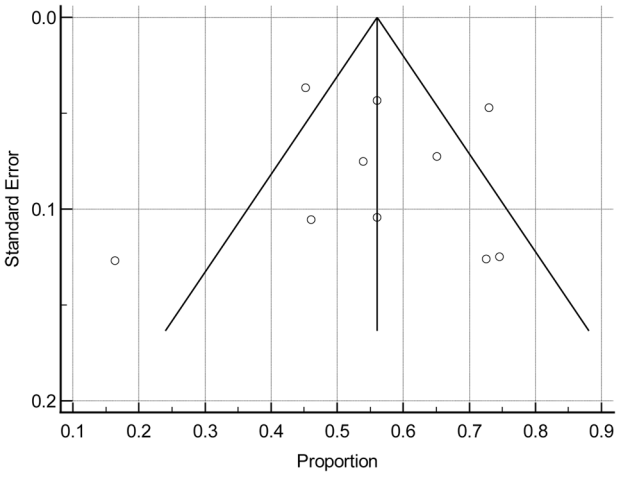

Figure 5. *Funnel plot of included studies for appendiceal adenocarcinoma from the meta-analysis.*

adequacy of follow-up were particularly poor in both study designs.

Please refer to Figure 5 and Figure 6 for funnel plots for included studies for appendiceal and colorectal adenocarcinoma, respectively, from the meta-analysis.

Results of syntheses. Following further exclusions, weighted percentages of elevated CEA (> 5 ng/ml or 5 μg/l) were 56 (95%CI=47-65) for appendiceal and 42 (95%CI=39-46) for colorectal adenocarcinoma (MD: 14; 95%CI=12-16; $p<0.0001$) (Table XII).

Reporting biases. The Egger bias test for the included studies was significant for those involving colorectal adenocarcinoma ($p=0.0054$); however, not significant for those that were appendiceal in origin ($p=0.90$). The Begg's test, however, yielded results for both that were not significant ($p=0.22$ and $p=0.93$, respectively).

Discussion

Summary of evidence. This systematic review and meta-analysis provided an extensive overview of patients with appendiceal and colorectal adenocarcinoma, comparing the proportion of them with an elevated CEA.

Weighted percentages of elevated CEA were significantly different between patients with appendiceal and those with colorectal adenocarcinoma (MD: 14; 95%CI=12-16; $p<0.0001$). Reasons behind this finding need further exploration as there are currently several theories surrounding the workings of CEA in patients with colorectal adenocarcinoma that can potentially cover those with appendiceal adenocarcinoma. These are discussed in the sections below.

Strengths and limitations. This is the first systematic review and meta-analysis comparing proportions of elevated CEA between patients with appendiceal and colorectal adenocarcinoma. This allows for a unique insight into the possible role of CEA not only in colorectal but also in appendiceal adenocarcinoma cases regarding liver metastases.

Limitations exist within this systematic review and meta-analysis chiefly regarding the methodological quality, study design, and a paucity of included studies for appendiceal adenocarcinoma. The overall methodological quality of the included studies was moderate for both appendiceal and colorectal adenocarcinoma. This means that the level of evidence behind conclusions drawn from this systematic review and meta-analysis potentially lacks external validity. In terms of study design, as there were no randomised-control trials available for inclusion, this allows for bias to be introduced and subsequently confound results. Lastly, with only 10 percent of the included studies involving appendiceal adenocarcinoma, it must be noted that the rarity of appendiceal adenocarcinoma cases and hence, the paucity of literature regarding this, makes comparison difficult.

How these results fit in with what is known. With this being the first systematic review and meta-analysis, there is little or no information available for comparison regarding the results of this study. However, it paves the way for future research regarding not only CEA but also appendiceal adenocarcinoma and how it varies from colorectal adenocarcinoma. The goal is to identify why there is such a disparity in the proportion of liver metastases between these two adenocarcinomas from different sites.

What this means for future research and practice. Plausible as the aforementioned hypothesis (3) may be, there needs to be further investigation by repeating the methodology presented by Tabuchi *et al*. (119) but in patients with appendiceal adenocarcinoma. Portal and peripheral vein samples of appendiceal adenocarcinoma patients are to be obtained and CEA levels compared using the exact methods described by Tabuchi *et al*. (119). If the hypothesis is correct, these values should be similar (or the portal venous CEA level should be lower than the peripheral vein CEA level). We have recently acquired full ethics approval for this to proceed at our institution and now actively recruiting suitable patients.

Another possibility that needs to be considered to explain the significant difference in the proportion of elevated CEA between appendiceal and colorectal adenocarcinoma is the possibility of mutations in the binding region (Pro-Glu-Leu-Pro-Lys; PELPK) of the CEA glycoprotein in patients with appendiceal adenocarcinoma. This has been explored in one study by Zimmer and Thomas (144) in 2001 in patients with colorectal cancer. They explored patients with elevated levels

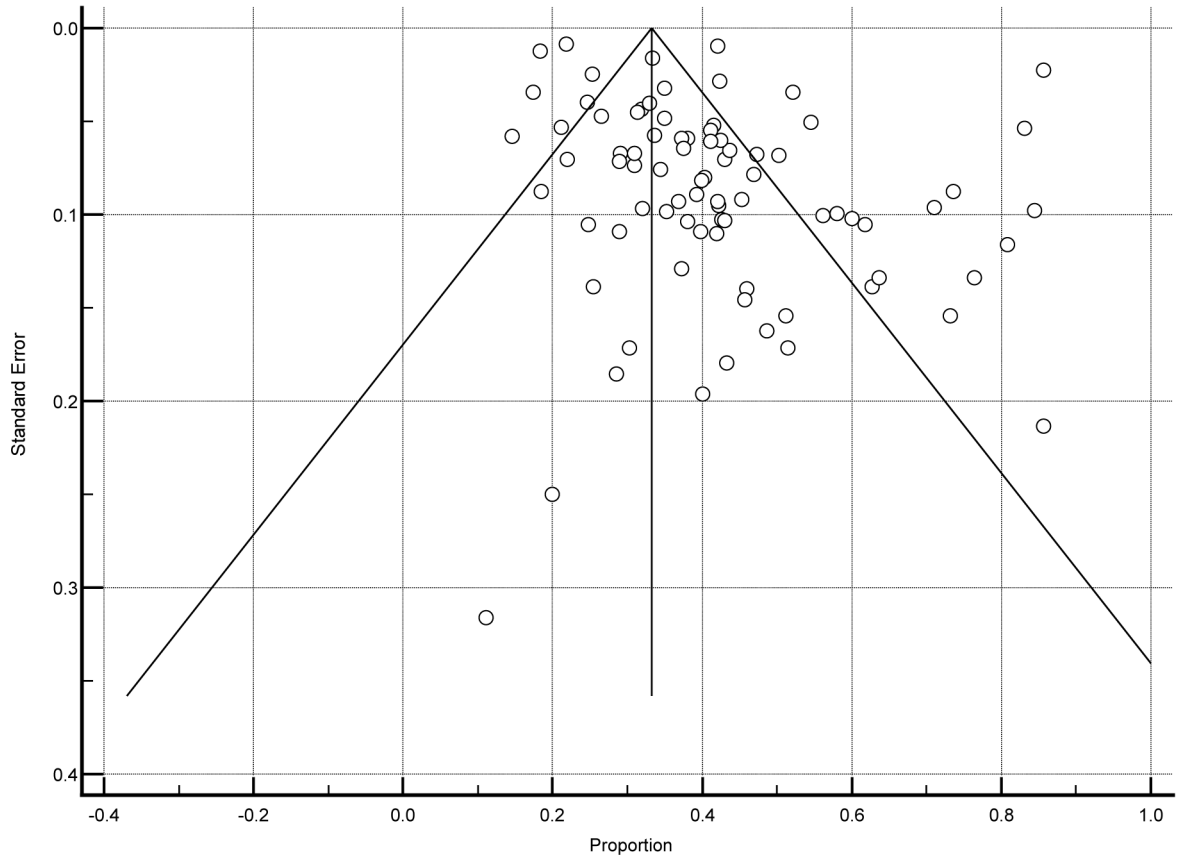

Figure 6. *Funnel plot for included studies for colorectal adenocarcinoma from the meta-analysis.*

Table XII. *Comparison between appendiceal and colorectal adenocarcinoma using the test of proportions for elevated carcinoembryonic antigen (CEA) (excluding studies involving low-grade appendiceal mucinous neoplasm and/or where the cut-off for CEA was not 5 ng/ml or 5 μg/l).*

Cancer type	Studies (n)	Patients (n)	% Elevated CEA	95% CI of the elevated CEA	Mean difference (%)	95% CI of the mean difference (%)	*p*-Value
Appendiceal[a]	10	2,458	56	47 to 65	14	12 to 16	<0.0001[b]
Colorectal[a]	83	54,759	42	39 to 46			
Total	93	57,217					

CI: Confidence interval. [a]Appendiceal: I^2=94%; Colorectal: I^2=99%; random effects modelling used. [b]Statistically significant result (p<0.05) for appendiceal when compared to colorectal adenocarcinoma.

of CEA and found mutations in their CEA, therefore there was a lower binding affinity of these patients' CEA to the receptors in the Kupffer cells. This meant that they did not seem to develop liver metastases, despite their highly elevated (peripheral) serum CEA levels. If these mutations were to be found in the CEA of patients with appendiceal adenocarcinoma, but in higher proportions, this may also account for the significantly lower proportion of liver metastases (145, 146).

Lastly, the release of CEA from colon cancer cells is dependent on phosphatidyl-specific phospholipase C as described by Sack *et al.* (147) in 1988. The resulting change in CEA from a membrane-bound, hydrophobic molecule to a soluble, hydrophilic molecule allows its inherent release from the cancer cells to travel throughout the circulation, as described above by Lee and Lee (2). If this was studied in appendiceal adenocarcinoma cells and phosphatidyl-specific phospholipase C was found to be lacking *in vivo*, it may

explain why although CEA is expressed in the majority of appendiceal adenocarcinomas (96), it may not correlate with serum levels of CEA and lack the flow-on effects that CEA would have as described by Lee and Lee (2) regarding liver metastases.

Conclusion

This systematic review and meta-analysis aimed to review studies involving patients with appendiceal and colorectal adenocarcinoma and compare the proportion of elevated CEA levels. In doing this, we have shown that there is a significantly higher proportion in patients with appendiceal adenocarcinoma. Reasons behind this finding have been presented and postulated.

Future research should focus on several areas. Firstly, a study comparing peripheral and portal venous blood samples of patients with appendiceal adenocarcinoma should be conducted. Regarding the possibility of PELPK region mutations in the CEA glycoprotein in patients with appendiceal adenocarcinoma, genomic sequencing of serum samples of patients with appendiceal and colorectal adenocarcinoma with elevated CEAs should be performed. Finally, studies should also focus on the presence or absence of phosphatidyl-specific phospholipase C in appendiceal adenocarcinoma cells, either *in vitro* or *in vivo*.

This will also allow for the potential for drug development regarding colorectal adenocarcinoma patients by blocking the effects of CEA and/or manipulation of the CEA receptor (by down-regulation) to reduce the development and recurrence of liver metastases.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study concept and design were carried out by Dr. Adam Cristaudo and his supervisor Prof. David Morris. Dr. Adam Cristaudo was involved in all aspects of the project. Dr. Scott Jennings was involved in independently reviewing articles, as well as performing data extraction and methodological assessment of the included studies. All Authors gave their approval for the article before submission.

References

1 Levine EA, Blazer DG 3rd, Kim MK, Shen P, Stewart JH 4th, Guy C and Hsu DS: Gene expression profiling of peritoneal metastases from appendiceal and colon cancer demonstrates unique biologic signatures and predicts patient outcomes. J Am Coll Surg *214(4)*: 599-606; discussion 606-7, 2012. PMID: 22342786. DOI: 10.1016/j.jamcollsurg.2011.12.028

2 Lee JH and Lee SW: The roles of carcinoembryonic antigen in liver metastasis and therapeutic approaches. Gastroenterol Res Pract *2017*: 7521987, 2017. PMID: 28588612. DOI: 10.1155/2017/7521987

3 Cristaudo AT and Morris DL: Hypothesis to explain the disparity in the proportion of liver metastases between appendiceal and colorectal cancer. Br J Surg *109(4)*: e63-e64, 2022. PMID: 35136948. DOI: 10.1093/bjs/znab472

4 Moher D, Liberati A, Tetzlaff J, Altman DG and PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med *151(4)*: 264-9, W64, 2009. PMID: 19622511. DOI: 10.7326/0003-4819-151-4-200908180-00135

5 Cristaudo AT, Jennings SB and Morris DL: Comparison of proportion of elevated carcinoembryonic antigen in patients with appendiceal and colorectal adenocarcinoma: A systematic review and meta-analysis. PROSPERO. 2021: CRD42021283615. Available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42021283615 [Last accessed on July 1, 2022]

6 Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2013. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.as [Last accessed on July 1, 2022]

7 MedCalc® Statistical Software version 20.022. MedCalc Software Ltd, Ostend, Belgium. Available at: https://www.medcalc.org [Last accessed on July 1, 2022]

8 Abe S, Kawai K, Ishihara S, Nozawa H, Hata K, Kiyomatsu T, Tanaka T and Watanabe T: Prognostic impact of carcinoembryonic antigen and carbohydrate antigen 19-9 in stage IV colorectal cancer patients after R0 resection. J Surg Res *205(2)*: 384-392, 2016. PMID: 27664887. DOI: 10.1016/j.jss.2016.06.078

9 Adachi Y, Mori M, Matsushima T, Kido A, Shimono R, Inoue T and Sugimachi K: The distribution of lymph node metastases in right-sided colon cancer. J Clin Gastroenterol *19(3)*: 210-213, 1994. PMID: 7806831. DOI: 10.1097/00004836-199410000-00008

10 Adrover E, Maestro ML, Sanz-Casla MT, del Barco V, Cerdán J, Fernández C and Balibrea JL: Expression of high p53 levels in colorectal cancer: a favourable prognostic factor. Br J Cancer *81(1)*: 122-126, 1999. PMID: 10487622. DOI: 10.1038/sj.bjc.6690660

11 Ahmed S, Pahwa P, Le D, Chalchal H, Chandra-Kanthan S, Iqbal N and Fields A: Primary tumor location and survival in the general population with metastatic colorectal cancer. Clin Colorectal Cancer *17(2)*: e201-e206, 2018. PMID: 29221688. DOI: 10.1016/j.clcc.2017.11.001

12 Akbulut H, Altuntas F, Akbulut KG, Ozturk G, Cindoruk M, Unal E and Icli F: Prognostic role of serum vascular endothelial growth factor, basic fibroblast growth factor and nitric oxide in patients with colorectal carcinoma. Cytokine *20(4)*: 184-190, 2002. PMID: 12543084. DOI: 10.1006/cyto.2002.1993

13 Al-Sarraf M, Baker L, Talley RW, Kithier K and Vaitkevicius VK: The value of serial carcinoembryonic antigen (CEA) in predicting response rate and survival of patients with gastrointestinal cancer treated with chemotherapy. Cancer *44(4)*: 1222-1225, 1979. PMID: 498010. DOI: 10.1002/1097-0142(197910)44:4<1222::aid-cncr2820440409>3.0.co;2-x

14 Aldulaymi B, Christensen IJ, Sölétormos G, Jess P, Nielsen SE, Laurberg S, Brünner N and Nielsen HJ: Chemoradiation-induced changes in serum CEA and plasma TIMP-1 in patients with locally advanced rectal cancer. Anticancer Res *30(11)*: 4755-4759, 2010. PMID: 21115936.

15 Alexander-Sefre F, Chandrakumaran K, Banerjee S, Sexton R, Thomas JM and Moran B: Elevated tumour markers prior to complete tumour removal in patients with pseudomyxoma peritonei predict early recurrence. Colorectal Dis *7(4)*: 382-386, 2005. PMID: 15932563. DOI: 10.1111/j.1463-1318.2005.00773.x

16 Alici S, Aykan NF, Sakar B, Bulutlar G, Kaytan E and Topuz E: Colorectal cancer in young patients: characteristics and outcome. Tohoku J Exp Med *199(2)*: 85-93, 2003. PMID: 12705353. DOI: 10.1620/tjem.199.85

17 Ayude D, Páez De La Cadena M, Martínez-Zorzano VS, Fernández-Briera A and Rodríguez-Berrocal FJ: Preoperative serum alpha-L-fucosidase activity as a prognostic marker in colorectal cancer. Oncology *64(1)*: 36-45, 2003. PMID: 12457030. DOI: 10.1159/000066521

18 Aziz O, Jaradat I, Chakrabarty B, Selvasekar CR, Fulford PE, Saunders MP, Renehan AG, Wilson MS and O'Dwyer ST: Predicting survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendix adenocarcinoma. Dis Colon Rectum *61(7)*: 795-802, 2018. PMID: 29771808. DOI: 10.1097/DCR.0000000000001076

19 Bai Z, Wang J, Wang T, Li Y, Zhao X, Wu G, Yang Y, Deng W and Zhang Z: Clinicopathologic parameters associated with postoperative complications and risk factors for tumor recurrence and mortality after tumor resection of patients with colorectal cancer. Clin Transl Oncol *20(2)*: 176-192, 2018. PMID: 28710725. DOI: 10.1007/s12094-017-1708-0

20 Bao F, Zhao LY, Balde AI, Liu H, Yan J, Li TT, Chen H and Li GX: Prognostic impact of lymph node skip metastasis in Stage III colorectal cancer. Colorectal Dis *18(9)*: O322-O329, 2016. PMID: 27438774. DOI: 10.1111/codi.13465

21 Baqar AR, Wilkins S, Staples M, Angus Lee CH, Oliva K and McMurrick P: The role of preoperative CEA in the management of colorectal cancer: A cohort study from two cancer centres. Int J Surg *64*: 10-15, 2019. PMID: 30822523. DOI: 10.1016/j.ijsu.2019.02.014

22 Baratti D, Kusamura S, Martinetti A, Seregni E, Laterza B, Oliva DG and Deraco M: Prognostic value of circulating tumor markers in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol *14(8)*: 2300-2308, 2007. PMID: 17510772. DOI: 10.1245/s10434-007-9393-9

23 Bhatavdekar JM, Patel DD, Chikhlikar PR, Shah NG, Vora HH, Ghosh N and Trivedi TI: Ectopic production of prolactin by colorectal adenocarcinoma. Dis Colon Rectum *44(1)*: 119-127, 2001. PMID: 11805572. DOI: 10.1007/BF02234833

24 Boey J, Cheung HC, Lai CK and Wong J: A prospective evaluation of serum carcinoembryonic antigen (CEA) levels in the management of colorectal carcinoma. World J Surg *8(3)*: 279-286, 1984. PMID: 6464483. DOI: 10.1007/BF01655052

25 Canbay E, Ishibashi H, Sako S, Mizumoto A, Hirano M, Ichinose M, Takao N and Yonemura Y: Preoperative carcinoembryonic antigen level predicts prognosis in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg *37(6)*: 1271-1276, 2013. PMID: 23467926. DOI: 10.1007/s00268-013-1988-7

26 Cardoso ML, Fernandes LC, Kim SB and Matos D: Relationship between peripheral and mesenteric serum levels of CEA and CA 242 with staging and histopathological variables in colorectal adenocarcinoma. Acta Cir Bras *24(5)*: 405-410, 2009. PMID: 19851695. DOI: 10.1590/s0102-86502009000500012

27 Carmignani CP, Hampton R, Sugarbaker CE, Chang D and Sugarbaker PH: Utility of CEA and CA 19-9 tumor markers in diagnosis and prognostic assessment of mucinous epithelial cancers of the appendix. J Surg Oncol *87(4)*: 162-166, 2004. PMID: 15334630. DOI: 10.1002/jso.20107

28 Carpelan-Holmström M, Louhimo J, Stenman UH, Alfthan H, Järvinen H and Haglund C: CEA, CA 242, CA 19-9, CA 72-4 and hCGbeta in the diagnosis of recurrent colorectal cancer. Tumour Biol *25(5-6)*: 228-234, 2004. PMID: 15627885. DOI: 10.1159/000081385

29 Carriquiry LA and Piñeyro A: Should carcinoembryonic antigen be used in the management of patients with colorectal cancer? Dis Colon Rectum *42(7)*: 921-929, 1999. PMID: 10411440. DOI: 10.1007/BF02237104

30 Carvalho TI, Novais PC, Lizarte FS Neto, Sicchieri RD, Rosa MS, Carvalho CA, Tirapelli DP, Peria FM, Rocha JJ and Féres O: Analysis of gene expression EGFR and KRAS, microRNA-21 and microRNA-203 in patients with colon and rectal cancer and correlation with clinical outcome and prognostic factors. Acta Cir Bras *32(3)*: 243-250, 2017. PMID: 28403349. DOI: 10.1590/S0102-865020170030000009

31 Chan CC, Fan CW, Kuo YB, Chen YH, Chang PY, Chen KT, Hung RP and Chan EC: Multiple serological biomarkers for colorectal cancer detection. Int J Cancer *126(7)*: 1683-1690, 2010. PMID: 19795454. DOI: 10.1002/ijc.24912

32 Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P, Koong AC, Kunz PA, Fisher GA, Ford JM, Welton M, Shelton A, Ma L, Arber DA and Pai RK: Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol *25(8)*: 1128-1139, 2012. PMID: 22481281. DOI: 10.1038/modpathol.2012.61

33 Chen P, Yao Y, Zhang D and Gu J: [Clinical characteristics and prognosis of colon cancer patient with extremely elevated carcinoembryonic antigen level]. Zhonghua Wei Chang Wai Ke Za Zhi *18(10)*: 1026-1031, 2015. PMID: 26499150.

34 Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, Chiang JM and Lin JR: Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis *27(10)*: 1347-1357, 2012. PMID: 22460305. DOI: 10.1007/s00384-012-1459-x

35 Cho YY, Kim JG, Chae YS, Sohn SK, Kang BW, Moon JH, Jeon SW, Park JS, Park JY and Choi GS: No Association of Insulin-like growth factor gene polymorphisms with survival in patients with colorectal cancer. Cancer Res Treat *43(3)*: 189-194, 2011. PMID: 22022297. DOI: 10.4143/crt.2011.43.3.189

36 Choi JY, Kim JG, Lee YJ, Chae YS, Sohn SK, Moon JH, Kang BW, Jung MK, Jeon SW, Park JS and Choi GS: Prognostic impact of polymorphisms in the CASPASE genes on survival

of patients with colorectal cancer. Cancer Res Treat *44(1)*: 32-36, 2012. PMID: 22500158. DOI: 10.4143/crt.2012.44.1.32

37 Chua TC, Liauw W and Morris DL: Early recurrence of pseudomyxoma peritonei following treatment failure of cytoreductive surgery and perioperative intraperitoneal chemotherapy is indicative of a poor survival outcome. Int J Colorectal Dis *27(3)*: 381-389, 2012. PMID: 21853235. DOI: 10.1007/s00384-011-1303-8

38 Cunningham L, Stocking B, Halter SA and Kalemeris G: Immunoperoxidase staining of carcinoembryonic antigen as a prognostic indicator in colorectal carcinoma. Dis Colon Rectum *29(2)*: 111-116, 1986. PMID: 3510834. DOI: 10.1007/BF02555392

39 Di Fabio F, Mehta A, Chandrakumaran K, Mohamed F, Cecil T and Moran B: Advanced pseudomyxoma peritonei requiring gastrectomy to achieve complete cytoreduction results in good long-term oncologic outcomes. Ann Surg Oncol *23(13)*: 4316-4321, 2016. PMID: 27380645. DOI: 10.1245/s10434-016-5389-7

40 Diez M, Pollan M, Müguerza JM, Gaspar MJ, Duce AM, Alvarez MJ, Ratia T, Herñandez P, Ruiz A and Granell J: Time-dependency of the prognostic effect of carcinoembryonic antigen and p53 protein in colorectal adenocarcinoma. Cancer *88(1)*: 35-41, 2000. PMID: 10618603. DOI: 10.1002/(sici)1097-0142(20000101)88:1<35::aid-cncr6>3.3.co;2-g

41 Dirican A, Kucukzeybek Y, Alacacioglu A, Varol U, Aksun S, Bayoglu IV, Demir L, Coban E, Sutcu R and Tarhan MO: Impact of pre-angiogenic factors on the treatment effect of bevacizumab in patients with metastatic colorectal cancer. Med Oncol *31(4)*: 905, 2014. PMID: 24596030. DOI: 10.1007/s12032-014-0905-8

42 Dragutinović VV, Radonjić NV, Petronijević ND, Tatić SB, Dimitrijević IB, Radovanović NS and Krivokapić ZV: Matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) in preoperative serum as independent prognostic markers in patients with colorectal cancer. Mol Cell Biochem *355(1-2)*: 173-178, 2011. PMID: 21541674. DOI: 10.1007/s11010-011-0851-0

43 Du C, Zhao J, Xue W, Dou F and Gu J: Prognostic value of microsatellite instability in sporadic locally advanced rectal cancer following neoadjuvant radiotherapy. Histopathology *62(5)*: 723-730, 2013. PMID: 23425253. DOI: 10.1111/his.12069

44 Fackche N, Schmocker RK, Kubi B, Cloyd JM, Ahmed A, Grotz T, Leiting J, Fournier K, Lee AJ, Powers B, Dineen S, Veerapong J, Baumgartner JM, Clarke C, Gamblin TC, Patel SH, Dhar V, Hendrix RJ, Lambert L, Abbott DE, Pokrzywa C, Lafaro K, Lee B, Zaidi MY, Maithel SK, Johnston FM and Greer JB: The utility of preoperative tumor markers in peritoneal carcinomatosis from primary appendiceal adenocarcinoma: an analysis from the US HIPEC collaborative. J Gastrointest Surg *25(11)*: 2908-2919, 2021. PMID: 33634422. DOI: 10.1007/s11605-021-04953-y

45 Forones NM, Tanaka M, Machado D, Falcão JB and Giovanoni M: Carcinoembryonic antigen in diagnosis and monitoring of colorectal cancer. Arq Gastroenterol *34(1)*: 3-6, 1997. PMID: 9458953.

46 Frikart L, Fournier K, Mach JP and Givel JC: Potential value of biliary CEA assay in early detection of colorectal adenocarcinoma liver metastases. Eur J Surg Oncol *21(3)*: 276-279, 1995. PMID: 7781796. DOI: 10.1016/s0748-7983(95)91459-5

47 Fu M, Chen D, Luo F, Li M, Wang Y, Chen J, Li A and Liu S: Association of the tumour stroma percentage in the preoperative biopsies with lymph node metastasis in colorectal cancer. Br J Cancer *122(3)*: 388-396, 2020. PMID: 31787749. DOI: 10.1038/s41416-019-0671-7

48 Gago T, Caldeira P, Cunha AC, Campelo P and Guerreiro H: Can we optimize CEA as a response marker in rectal cancer? Rev Esp Enferm Dig *113(6)*: 423-428, 2021. PMID: 33228364. DOI: 10.17235/reed.2020.7321/2020

49 Gao C, Li JT, Fang L, Xu YY and Zhao HC: Drug allergy and the risk of lymph node metastasis in rectal cancer. PLoS One *9(8)*: e106123, 2014. PMID: 25162236. DOI: 10.1371/journal.pone.0106123

50 Gasser M, Gerstlauer C, Grimm M, Bueter M, Lebedeva T, Lutz J, Maeder U, Ribas C, Ribas C, Nichiporuk E, Thalheimer A, Heemann U, Thiede A, Meyer D and Waaga-Gasser AM: Comparative analysis of predictive biomarkers for therapeutical strategies in colorectal cancer. Ann Surg Oncol *14(4)*: 1272-1284, 2007. PMID: 17211733. DOI: 10.1245/s10434-006-9155-0

51 Germá-Lluch JR, Alvarez I, Carrió I, Nogueras FM, Marcuello E, Estorch M and Berná L: Radioimmunolocalization of colorectal carcinoma. A correlation among RIL results, surgical findings, serum tumor marker levels and the presence of CEA and CA 19.9 in tumor tissue: the experience of the Hospital de la Santa Creu i Sant Pau. Ann Oncol *2(6)*: 409-415, 1991. PMID: 1768627. DOI: 10.1093/oxfordjournals.annonc.a057975

52 Goslin R, O'Brien MJ, Steele G, Mayer R, Wilson R, Corson JM and Zamcheck N: Correlation of Plasma CEA and CEA tissue staining in poorly differentiated colorectal cancer. Am J Med *71(2)*: 246-253, 1981. PMID: 6167166. DOI: 10.1016/0002-9343(81)90125-x

53 Guadagni F, Roselli M, Cosimelli M, Mannella E, Tedesco M, Cavaliere F, Grassi A, Abbolito MR, Greiner JW and Schlom J: TAG-72 (CA 72-4 assay) as a complementary serum tumor antigen to carcinoembryonic antigen in monitoring patients with colorectal cancer. Cancer *72(7)*: 2098-2106, 1993. PMID: 8374868. DOI: 10.1002/1097-0142(19931001)72:7<2098::aid-cncr2820720707>3.0.co;2-g

54 Gunawardene A, Larsen P, Shekouh A and Dennett E: Pre-operative carcinoembryonic antigen predicts survival following colorectal cancer surgery with curative intent. ANZ J Surg *88(12)*: 1311-1315, 2018. PMID: 30066426. DOI: 10.1111/ans.14723

55 Hamada Y, Yamamura M, Hioki K, Yamamoto M, Nagura H and Watanabe K: Immunohistochemical study of carcinoembryonic antigen in patients with colorectal cancer. Correlation with plasma carcinoembryonic antigen levels. Cancer *55(1)*: 136-141, 1985. PMID: 3880653. DOI: 10.1002/1097-0142(19850101)55:1<136::aid-cncr2820550121>3.0.co;2-p

56 Han SX, Wang J, Wang LJ, Jin GH, Ying X, He CC, Guo XJ, Zhang JY, Zhang Y and Zhu Q: The role of RCAS1 as a biomarker in diagnosing CRC and monitoring tumor recurrence and metastasis. Tumour Biol *35(6)*: 6149-6157, 2014. PMID: 24652591. DOI: 10.1007/s13277-014-1814-3

57 Hotta T, Takifuji K, Uchiyama K, Yokoyama S, Matsuda K, Higashiguchi T, Tominaga T, Oku Y, Nasu T and Yamaue H: Potential predictors of survival after surgery for colorectal cancer patients with synchronous unresectable liver metastases. Oncol Rep *16(6)*: 1369-1374, 2006. PMID: 17089063. DOI: 10.3892/or.16.6.1369

58 Huang CS, Lin JK, Wang LW, Liang WY, Lin CC, Lan YT, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC and Chang SC: Assessment of the value of carcinoembryonic antigen reduction

ratio as a prognosis factor in rectal cancer. Am J Surg *208(1)*: 99-105, 2014. PMID: 24524862. DOI: 10.1016/j.amjsurg.2013.08.054

59 Huang Q, Zou MH, Jiang Y, Chen ZP, Wang Q, Wei JC, Li WL and Cao J: Outcomes of laparoscopic surgery for mucinous colorectal adenocarcinoma. J Laparoendosc Adv Surg Tech A *31(6)*: 638-647, 2021. PMID: 33151807. DOI: 10.1089/lap.2020.0588

60 Hung HY, Chen JS, Chien-YuhYeh, Tang R, Hsieh PS, Wen-SyTasi, You YT, You JF and Chiang JM: Preoperative alkaline phosphatase elevation was associated with poor survival in colorectal cancer patients. Int J Colorectal Dis *32(12)*: 1775-1778, 2017. PMID: 29030683. DOI: 10.1007/s00384-017-2907-4

61 Huo YR, Huang Y, Liauw W, Zhao J and Morris DL: Prognostic value of carcinoembryonic antigen (CEA), AFP, CA19-9 and CA125 for patients with colorectal cancer with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Anticancer Res *36(3)*: 1041-1049, 2016. PMID: 26976996.

62 Iarŭmov N, Ignatov A and Viiachki I: [The pre- and postoperative monitoring of the immunological indices and tumor markers in colorectal carcinoma]. Khirurgiia (Sofiia) *51(3)*: 42-48, 1998. PMID: 9974027.

63 A collaborative study of a test for carcinoembryonic antigen (CEA) in the sera of patients with carcinoma of the colon and rectum. A joint National Cancer Institute of Canada-American Cancer Society investigation. Can Med Assoc J *107(1)*: 25-33, 1972. PMID: 5042884.

64 Ishiguro S, Akasu T, Fujita S, Yamamoto S, Kusters M and Moriya Y: Pelvic exenteration for clinical T4 rectal cancer: oncologic outcome in 93 patients at a single institution over a 30-year period. Surgery *145(2)*: 189-195, 2009. PMID: 19167974. DOI: 10.1016/j.surg.2008.09.014

65 Ishizuka D, Shirai Y, Sakai Y and Hatakeyama K: Colorectal carcinoma liver metastases: clinical significance of preoperative measurement of serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels. Int J Colorectal Dis *16(1)*: 32-37, 2001. PMID: 11317695. DOI: 10.1007/s003840000268

66 Ishizuka M, Nagata H, Takagi K and Kubota K: Systemic inflammatory response associated with distant metastasis of T1 or T2 colorectal cancer. Dig Dis Sci *55(11)*: 3181-3187, 2010. PMID: 20198429. DOI: 10.1007/s10620-010-1159-8

67 Jang KY, Kim YN, Bae JS, Chung MJ, Moon WS, Kang MJ, Lee DG and Park HS: Expression of Cyclin D1 is associated with β-catenin expression and correlates with good prognosis in colorectal adenocarcinoma. Transl Oncol *5(5)*: 370-378, 2012. PMID: 23066445. DOI: 10.1593/tlo.12220

68 Järvinen P, Ristimäki A, Kantonen J and Lepistö A: Feasibility of radical cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei of appendiceal origin. Scand J Surg *102(3)*: 145-151, 2013. PMID: 23963027. DOI: 10.1177/1457496913490463

69 Jensen LH, Lindebjerg J, Crüger DG, Brandslund I, Jakobsen A, Kolvraa S and Nielsen JN: Microsatellite instability and the association with plasma homocysteine and thymidylate synthase in colorectal cancer. Cancer Invest *26(6)*: 583-589, 2008. PMID: 18584349. DOI: 10.1080/07357900801970992

70 Jones C, Badger SA, Epanomeratikis E, McKie LD, Diamond T and Taylor MA: Role of carcinoembryonic antigen as a marker for colorectal liver metastases. Br J Biomed Sci *70(2)*: 47-50, 2013. PMID: 23888604. DOI: 10.1080/09674845.2013.11669934

71 Jubert AV, Talbott TM and Maycroft TM: Characteristics of adenocarcinomas of the colorectum with low levels of preoperative plasma carcinoembryonic antigen (CEA). Cancer *42(2)*: 635-639, 1978. PMID: 679156. DOI: 10.1002/1097-0142(197808)42:2<635::aid-cncr2820420234>3.0.co;2-b

72 Kang H, Min BS, Lee KY, Kim NK, Kim SN, Choi J and Kim H: Loss of E-cadherin and MUC2 expressions correlated with poor survival in patients with stages II and III colorectal carcinoma. Ann Surg Oncol *18(3)*: 711-719, 2011. PMID: 20865330. DOI: 10.1245/s10434-010-1338-z

73 Khan MA, Maken RN, Nisar H, Fatima I, Khan IU, Masood M and Shahid AB: THE Role of Preoperative carcinoembryonic antigen in recurrence of resectable colorectal carcinoma. Acta Clin Croat *59(2)*: 216-222, 2020. PMID: 33456107. DOI: 10.20471/acc.2020.59.02.03

74 Kim CW, Yoon YS, Park IJ, Lim SB, Yu CS and Kim JC: Elevation of preoperative s-CEA concentration in stage IIA colorectal cancer can also be a high risk factor for stage II patients. Ann Surg Oncol *20(9)*: 2914-2920, 2013. PMID: 23760586. DOI: 10.1245/s10434-013-2919-4

75 Kim JG, Chae YS, Lee SJ, Kang BW, Park JY, Lee EJ, Jeon HS, Park JS and Choi GS: Genetic variation in microRNA-binding site and prognosis of patients with colorectal cancer. J Cancer Res Clin Oncol *141(1)*: 35-41, 2015. PMID: 25079514. DOI: 10.1007/s00432-014-1780-6

76 Kuo YB, Chan CC, Chang CA, Fan CW, Hung RP, Hung YS, Chen KT, Yu JS, Chang YS and Chan EC: Identification of phospholipid scramblase 1 as a biomarker and determination of its prognostic value for colorectal cancer. Mol Med *17(1-2)*: 41-47, 2011. PMID: 20927484. DOI: 10.2119/molmed.2010.00115

77 Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, Park KJ, Roh MS, Kim SG, Kim HJ and Lee JH: Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers *17(3)*: 216-222, 2012. PMID: 22424597. DOI: 10.3109/1354750X.2012.656705

78 Kwon KA, Kim SH, Oh SY, Lee S, Han JY, Kim KH, Goh RY, Choi HJ, Park KJ, Roh MS, Kim HJ, Kwon HC and Lee JH: Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. BMC Cancer *10*: 203, 2010. PMID: 20465852. DOI: 10.1186/1471-2407-10-203

79 Lee JH, Hyun JH, Kim DY, Yoo BC, Park JW, Kim SY, Chang HJ, Kim BC, Kim TH, Oh JH and Sohn DK: The role of fibrinogen as a predictor in preoperative chemoradiation for rectal cancer. Ann Surg Oncol *22(1)*: 209-215, 2015. PMID: 25384698. DOI: 10.1245/s10434-014-3962-5

80 Leu SY and Wang SR: Clinical significance of arginase in colorectal cancer. Cancer *70(4)*: 733-736, 1992. PMID: 1643605. DOI: 10.1002/1097-0142(19920815)70:4<733::aid-cncr2820700403>3.0.co;2-6

81 Li Y, Liu W, Zhou Z, Ge H, Zhao L, Liu H, Song X, Wang D, Pei Q and Tan F: Development and validation of prognostic nomograms for early-onset locally advanced colon cancer. Aging (Albany NY) *13(1)*: 477-492, 2020. PMID: 33289705. DOI: 10.18632/aging.202157

82 Liang JT, Huang KC, Cheng YM, Hsu HC, Cheng AL, Hsu CH, Yeh KH, Wang SM and Chang KJ: P53 overexpression predicts poor chemosensitivity to high-dose 5-fluorouracil plus leucovorin chemotherapy for stage IV colorectal cancers after

palliative bowel resection. Int J Cancer *97(4)*: 451-457, 2002. PMID: 11802206. DOI: 10.1002/ijc.1637

83 Liu GC, Zhang X, Xie E, An X, Cai PQ, Zhu Y, Tang JH, Kong LH, Lin JZ, Pan ZZ and Ding PR: The value of restaging with chest and abdominal CT/MRI scan after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Medicine (Baltimore) *94(47)*: e2074, 2015. PMID: 26632714. DOI: 10.1097/MD.0000000000002074

84 Liu H, Cui Y, Shen W, Fan X, Cui L, Zhang C, Ren G, Fu J and Wang D: Pretreatment magnetic resonance imaging of regional lymph nodes with carcinoembryonic antigen in prediction of synchronous distant metastasis in patients with rectal cancer. Oncotarget *7(19)*: 27199-27207, 2016. PMID: 27070083. DOI: 10.18632/oncotarget.7979

85 Livingstone AS, Hampson LG, Shuster J, Gold P and Hinchey EJ: Carcinoembryonic antigen in the diagnosis and management of colorectal carcinoma. Current status. Arch Surg *109(2)*: 259-264, 1974. PMID: 4846441. DOI: 10.1001/archsurg.1974.01360020119023

86 Ma R, Wang B, Zhai X, Lu Y and Xu H: Management and prognostic prediction of appendiceal mucinous adenocarcinoma with peritoneal metastasis: a single center study in China. BMC Cancer *20(1)*: 280, 2020. PMID: 32252683. DOI: 10.1186/s12885-020-06787-4

87 Machida N, Yoshino T, Boku N, Hironaka S, Onozawa Y, Fukutomi A, Yamazaki K, Yasui H, Taku K and Asaka M: Impact of baseline sum of longest diameter in target lesions by RECIST on survival of patients with metastatic colorectal cancer. Jpn J Clin Oncol *38(10)*: 689-694, 2008. PMID: 18845522. DOI: 10.1093/jjco/hyn086

88 Meling GI, Rognum TO, Clausen OP, Børmer O, Lunde OC, Schlichting E, Grüner OP, Hognestad J, Trondsen E and Havig O: Serum carcinoembryonic antigen in relation to survival, DNA ploidy pattern, and recurrent disease in 406 colorectal carcinoma patients. Scand J Gastroenterol *27(12)*: 1061-1068, 1992. PMID: 1475624. DOI: 10.3109/00365529209028139

89 Melli F, Bartolini I, Risaliti M, Tucci R, Ringressi MN, Muiesan P, Taddei A and Amedei A: Evaluation of prognostic factors and clinicopathological patterns of recurrence after curative surgery for colorectal cancer. World J Gastrointest Surg *13(1)*: 50-75, 2021. PMID: 33552394. DOI: 10.4240/wjgs.v13.i1.50

90 Miyake H, Murono K, Nagata H, Nozawa H, Kawai K, Hata K, Tanaka T, Nishikawa T, Shuno Y, Sasaki K and Ishihara S: Prognostic significance of doubling time in patients undergoing radical surgery for metachronous peritoneal metastases of colorectal cancer. Int J Colorectal Dis *34(5)*: 801-809, 2019. PMID: 30739186. DOI: 10.1007/s00384-019-03259-5

91 Morita S, Nomura T, Fukushima Y, Morimoto T, Hiraoka N and Shibata N: Does serum CA19-9 play a practical role in the management of patients with colorectal cancer? Dis Colon Rectum *47(2)*: 227-232, 2004. PMID: 15043294. DOI: 10.1007/s10350-003-0041-6

92 Myerson RJ, Michalski JM, King ML, Birnbaum E, Fleshman J, Fry R, Kodner I, Lacey D and Lockett MA: Adjuvant radiation therapy for rectal carcinoma: predictors of outcome. Int J Radiat Oncol Biol Phys *32(1)*: 41-50, 1995. PMID: 7721638. DOI: 10.1016/0360-3016(94)00493-5

93 Nakagoe T, Sawai T, Tsuji T, Jibiki M, Nanashima A, Yamaguchi H, Kurosaki N, Yasutake T and Ayabe H: Circulating sialyl Lewis(x), sialyl Lewis(a), and sialyl Tn antigens in colorectal cancer patients: multivariate analysis of predictive factors for serum antigen levels. J Gastroenterol *36(3)*: 166-172, 2001. PMID: 11291879. DOI: 10.1007/s005350170124

94 Nakamura Y, Shida D, Tanabe T, Takamizawa Y, Imaizumi J, Ahiko Y, Sakamoto R, Moritani K, Tsukamoto S and Kanemitsu Y: Prognostic impact of preoperatively elevated and postoperatively normalized carcinoembryonic antigen levels following curative resection of stage I-III rectal cancer. Cancer Med *9(2)*: 653-662, 2020. PMID: 31799750. DOI: 10.1002/cam4.2758

95 Nozoe T, Mori E, Takahashi I and Ezaki T: Preoperative elevation of serum C-reactive protein as an independent prognostic indicator of colorectal carcinoma. Surg Today *38(7)*: 597-602, 2008. PMID: 18612783. DOI: 10.1007/s00595-007-3680-8

96 Nummela P, Leinonen H, Järvinen P, Thiel A, Järvinen H, Lepistö A and Ristimäki A: Expression of CEA, CA19-9, CA125, and EpCAM in pseudomyxoma peritonei. Hum Pathol *54*: 47-54, 2016. PMID: 27038681. DOI: 10.1016/j.humpath.2016.02.022

97 Oñate-Ocaña LF, Montesdeoca R, López-Graniel CM, Aiello-Crocifoglio V, Mondragón-Sánchez R, Cortina-Borja M, Herrera-Goepfert R, Oros-Ovalle C and Gallardo-Rincón D: Identification of patients with high-risk lymph node-negative colorectal cancer and potential benefit from adjuvant chemotherapy. Jpn J Clin Oncol *34(6)*: 323-328, 2004. PMID: 15333684. DOI: 10.1093/jjco/hyh054

98 Ooi BS, Ho YH, Eu KW and Seow Choen F: Primary colorectal signet-ring cell carcinoma in Singapore. ANZ J Surg *71(12)*: 703-706, 2001. PMID: 11906382. DOI: 10.1046/j.1445-1433.2001.02269.x

99 Painbeni T, Gamelin E, Cailleux A, Le Bouil A, Boisdron-Celle M, Daver A, Larra F and Allain P: Plasma sialic acid as a marker of the effect of the treatment on metastatic colorectal cancer. Eur J Cancer *33(13)*: 2216-2220, 1997. PMID: 9470809. DOI: 10.1016/s0959-8049(97)00318-3

100 Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, Lee WY and Chun HK: Prognostic comparison between mucinous and nonmucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore) *94(15)*: e658, 2015. PMID: 25881840. DOI: 10.1097/MD.0000000000000658

101 Pedrazzani C, Turri G, Mantovani G, Conti C, Ziello R, Conci S, Campagnaro T, Ruzzenente A and Guglielmi A: Prognostic value of thrombocytosis in patients undergoing surgery for colorectal cancer with synchronous liver metastases. Clin Transl Oncol *21(12)*: 1644-1653, 2019. PMID: 30937817. DOI: 10.1007/s12094-019-02093-z

102 Peng J, Lin J, Qiu M, Wu X, Lu Z, Chen G, Li L, Ding P, Gao Y, Zeng Z, Zhang H, Wan D and Pan Z: Clinical factors of post-chemoradiotherapy as valuable indicators for pathological complete response in locally advanced rectal cancer. Clinics (Sao Paulo) *71(8)*: 449-454, 2016. PMID: 27626475. DOI: 10.6061/clinics/2016(08)07

103 Petrelli NJ, Hanna S, Rodriguez-Bigas M and Anderson G: The use of the major anoxic stress response protein P34, the K isozyme of lactate dehydrogenase, and carcinoembryonic antigen in the follow-up of patients with colorectal adenocarcinoma. Cancer *70(7)*: 1834-1837, 1992. PMID: 1525757. DOI: 10.1002/1097-0142(19921001)70:7<1834::aid-cncr2820700704>3.0.co;2-v

104 Plebani M, De Paoli M, Basso D, Roveroni G, Giacomini A, Galeotti F and Corsini A: Serum tumor markers in colorectal

cancer staging, grading, and follow-up. J Surg Oncol *62(4)*: 239-244, 1996. PMID: 8691835. DOI: 10.1002/(SICI)1096-9098(199608)62:4<239::AID-JSO2>3.0.CO;2-7

105 Quah HM, Chou JF, Gonen M, Shia J, Schrag D, Landmann RG, Guillem JG, Paty PB, Temple LK, Wong WD and Weiser MR: Identification of patients with high-risk stage II colon cancer for adjuvant therapy. Dis Colon Rectum *51(5)*: 503-507, 2008. PMID: 18322753. DOI: 10.1007/s10350-008-9246-z

106 Ratto C, Sofo L, Ippoliti M, Merico M, Doglietto GB and Crucitti F: Prognostic factors in colorectal cancer. Literature review for clinical application. Dis Colon Rectum *41(8)*: 1033-1049, 1998. PMID: 9715162. DOI: 10.1007/BF02237397

107 Rosati G, Rossi A, Reggiardo G and Manzione L: A phase II study of irinotecan alternated with a weekly schedule of high-dose leucovorin and 48-hour 5-fluorouracil infusion in patients with metastatic colorectal cancer. Oncology *62(3)*: 209-215, 2002. PMID: 12065867. DOI: 10.1159/000059567

108 Roselli M, Guadagni F, Martini F, Spila A, Mariotti S, D'Alessandro R, Aloe S, Gazzaniga PP, Basili S, Cosimelli M and Ferroni P: Association between serum carcinoembryonic antigen and endothelial cell adhesion molecules in colorectal cancer. Oncology *65(2)*: 132-138, 2003. PMID: 12931019. DOI: 10.1159/000072338

109 Sastre J, Maestro ML, Puente J, Veganzones S, Alfonso R, Rafael S, García-Saenz JA, Vidaurreta M, Martín M, Arroyo M, Sanz-Casla MT and Díaz-Rubio E: Circulating tumor cells in colorectal cancer: correlation with clinical and pathological variables. Ann Oncol *19(5)*: 935-938, 2008. PMID: 18212090. DOI: 10.1093/annonc/mdm583

110 Schneider HJ, Sampson SA, Cunningham D, Norman AR, Andreyev HJ, Tilsed JV and Clarke PA: Bcl-2 expression and response to chemotherapy in colorectal adenocarcinomas. Br J Cancer *75(3)*: 427-431, 1997. PMID: 9020491. DOI: 10.1038/bjc.1997.70

111 Selcukbiricik F, Bilici A, Tural D, Erdamar S, Soyluk O, Buyukunal E, Demirelli F and Serdengecti S: Are high initial CEA and CA 19-9 levels associated with the presence of K-ras mutation in patients with metastatic colorectal cancer? Tumour Biol *34(4)*: 2233-2239, 2013. PMID: 23625655. DOI: 10.1007/s13277-013-0763-6

112 Seo Y, Matozaki T, Tsuda M, Hayashi Y, Itoh H and Kasuga M: Overexpression of SAP-1, a transmembrane-type protein tyrosine phosphatase, in human colorectal cancers. Biochem Biophys Res Commun *231(3)*: 705-711, 1997. PMID: 9070877. DOI: 10.1006/bbrc.1997.6139

113 Shen ZY, Fang Y, Zhen L, Zhu XJ, Chen H, Liu H, Jiang B, Li GX and Deng HJ: Analysis of the predictive efficiency of S100P on adverse prognosis and the pathogenesis of S100P-mediated invasion and metastasis of colon adenocarcinoma. Cancer Genet *209(4)*: 143-153, 2016. PMID: 26975699. DOI: 10.1016/j.cancergen.2016.02.002

114 Shida D, Hamaguchi T, Ochiai H, Tsukamoto S, Takashima A, Boku N and Kanemitsu Y: Prognostic impact of palliative primary tumor resection for unresectable Stage 4 colorectal cancer: Using a propensity score analysis. Ann Surg Oncol *23(11)*: 3602-3608, 2016. PMID: 27272107. DOI: 10.1245/s10434-016-5299-8

115 Shiue JW, Tam TN, Lai KH, Jeng FS, Liu RS, Yeh SH, Lee SD and Tsai YT: The clinical significance of a new monoclonal antibody defined antigen CA195 as a tumor marker in colorectal cancer. Zhonghua Yi Xue Za Zhi (Taipei) *44(4)*: 223-228, 1989. PMID: 2634457.

116 Sisik A, Kaya M, Bas G, Basak F and Alimoglu O: CEA and CA 19-9 are still valuable markers for the prognosis of colorectal and gastric cancer patients. Asian Pac J Cancer Prev *14(7)*: 4289-4294, 2013. PMID: 23991991. DOI: 10.7314/apjcp.2013.14.7.4289

117 Sohn DK, Han KS, Kim BC, Hong CW, Chang HJ, Baek JY, Kim MJ, Park SC, Oh JH and Kim DY: Endoscopic assessment of tumor regression after preoperative chemoradiotherapy as a prognostic marker in locally advanced rectal cancer. Surg Oncol *26(4)*: 453-459, 2017. PMID: 29113665. DOI: 10.1016/j.suronc.2017.09.002

118 Suwanagool P, Fujimori T and Maeda S: Value of tissue carcinoembryonic antigen in patients with colorectal carcinoma. Asian Pac J Allergy Immunol *8(1)*: 33-37, 1990. PMID: 2168182.

119 Tabuchi Y, Deguchi H and Saitoh Y: Carcinoembryonic antigen and carbohydrate antigen 19-9 levels of peripheral and draining venous blood in colorectal cancer patients. Correlation with histopathologic and immunohistochemical variables. Cancer *62(8)*: 1605-1613, 1988. PMID: 3167774. DOI: 10.1002/1097-0142(19881015)62:8<1605::aid-cncr2820620825>3.0.co;2-v

120 Takagawa R, Fujii S, Ohta M, Nagano Y, Kunisaki C, Yamagishi S, Osada S, Ichikawa Y and Shimada H: Preoperative serum carcinoembryonic antigen level as a predictive factor of recurrence after curative resection of colorectal cancer. Ann Surg Oncol *15(12)*: 3433-3439, 2008. PMID: 18846401. DOI: 10.1245/s10434-008-0168-8

121 Takakura Y, Ikeda S, Imaoka Y, Urushihara T and Itamoto T: An elevated preoperative serum carbohydrate antigen 19-9 level is a significant predictor for peritoneal dissemination and poor survival in colorectal cancer. Colorectal Dis *17(5)*: 417-425, 2015. PMID: 25512077. DOI: 10.1111/codi.12865

122 Takeda A, Otani Y, Iseki H, Takeuchi H, Aikawa K, Tabuchi S, Shinozuka N, Saeki T, Okazaki Y and Koyama I: Clinical significance of large tenascin-C spliced variant as a potential biomarker for colorectal cancer. World J Surg *31(2)*: 388-394, 2007. PMID: 17219282. DOI: 10.1007/s00268-006-0328-6

123 Tan KL, Tan WS, Lim JF and Eu KW: Krukenberg tumors of colorectal origin: a dismal outcome—experience of a tertiary center. Int J Colorectal Dis *25(2)*: 233-238, 2010. PMID: 19705132. DOI: 10.1007/s00384-009-0796-x

124 Thirunavukarasu P, Sathaiah M, Singla S, Sukumar S, Karunamurthy A, Pragatheeshwar KD, Lee KK, Zeh H 3rd, Kane KM and Bartlett DL: Medullary carcinoma of the large intestine: a population based analysis. Int J Oncol *37(4)*: 901-907, 2010. PMID: 20811712. DOI: 10.3892/ijo_00000741

125 Toiyama Y, Miki C, Inoue Y, Okugawa Y, Koike Y, Yokoe T, Tanaka K and Kusunoki M: Soluble intercellular adhesion molecule-1 as a prognostic marker for stage II colorectal cancer patients. Ann Surg Oncol *15(6)*: 1617-1624, 2008. PMID: 18368454. DOI: 10.1245/s10434-008-9874-5

126 Tsai WS, Changchien CR, Yeh CY, Chen JS, Tang R, Chiang JM, Hsieh PS, Fan CW and Wang JY: Preoperative plasma vascular endothelial growth factor but not nitrite is a useful complementary tumor marker in patients with colorectal cancer. Dis Colon Rectum *49(6)*: 883-894, 2006. PMID: 16741643. DOI: 10.1007/s10350-006-0528-z

127 Uejima C, Saito H, Tada Y, Tanio A, Murakami Y, Yamamoto M, Matsunaga T, Fukumoto Y, Tokuyasu N, Takano S, Sakamoto T, Honjo S and Fujiwara Y: The combination of

prognostic nutritional indicator and serum carcinoembryonic antigen is useful in predicting postoperative recurrence in Stage II colorectal cancer. Yonago Acta Med *64(2)*: 176-183, 2021. PMID: 34025192. DOI: 10.33160/yam.2021.05.009

128 van Eden WJ, Kok NFM, Snaebjornsson P, Jóźwiak K, Woensdregt K, Bottenberg PD, Boot H and Aalbers AGJ: Factors influencing long-term survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei originating from appendiceal neoplasms. BJS Open *3(3)*: 376-386, 2019. PMID: 31183454. DOI: 10.1002/bjs5.50134

129 van Ruth S, Acherman YI, van de Vijver MJ, Hart AA, Verwaal VJ and Zoetmulder FA: Pseudomyxoma peritonei: a review of 62 cases. Eur J Surg Oncol *29(8)*: 682-688, 2003. PMID: 14511618. DOI: 10.1016/s0748-7983(03)00149-5

130 Wagner PL, Austin F, Sathaiah M, Magge D, Maduekwe U, Ramalingam L, Jones HL, Holtzman MP, Ahrendt SA, Zureikat AH, Pingpank JF, Zeh HJ 3rd, Bartlett DL and Choudry HA: Significance of serum tumor marker levels in peritoneal carcinomatosis of appendiceal origin. Ann Surg Oncol *20(2)*: 506-514, 2013. PMID: 22941175. DOI: 10.1245/s10434-012-2627-5

131 Waisberg J, Contim-Neto L, Oliveira Mda S, Matheus Cde O, Nagashima CA and Goffi FS: Determination of carcinoembryonic antigen levels in peripheral and draining venous blood in patients with colorectal carcinoma. Arq Gastroenterol *41(2)*: 88-92, 2004. PMID: 15543380. DOI: 10.1590/s0004-28032004000200004

132 Wang L, Zhong XG, Peng YF, Li ZW and Gu J: Prognostic value of pretreatment level of carcinoembryonic antigen on tumour downstaging and early occurring metastasis in locally advanced rectal cancer following neoadjuvant radiotherapy (30 Gy in 10 fractions). Colorectal Dis *16(1)*: 33-39, 2014. PMID: 23848511. DOI: 10.1111/codi.12354

133 Wang WS, Lin JK, Chiou TJ, Liu JH, Fan FS, Yen CC, Lin TC, Jiang JK, Yang SH, Wang HS and Chen PM: Preoperative carcinoembryonic antigen level as an independent prognostic factor in colorectal cancer: Taiwan experience. Jpn J Clin Oncol *30(1)*: 12-16, 2000. PMID: 10770562. DOI: 10.1093/jjco/hyd003

134 Webb A, Scott-Mackie P, Cunningham D, Norman A, Andreyev J, O'Brien M and Bensted J: The prognostic value of CEA, beta HCG, AFP, CA125, CA19-9 and C-erb B-2, beta HCG immunohistochemistry in advanced colorectal cancer. Ann Oncol *6(6)*: 581-587, 1995. PMID: 8573538. DOI: 10.1093/oxfordjournals.annonc.a059248

135 Weihrauch MR, Skibowski E, Koslowsky TC, Voiss W, Re D, Kuhn-Regnier F, Bannwarth C, Siedek M, Diehl V and Bohlen H: Immunomagnetic enrichment and detection of micrometastases in colorectal cancer: correlation with established clinical parameters. J Clin Oncol *20(21)*: 4338-4343, 2002. PMID: 12409333. DOI: 10.1200/JCO.2002.02.152

136 Yang PC, Lin BR, Chen YC, Lin YL, Lai HS, Huang KW and Liang JT: Local control by radiofrequency thermal ablation increased overall survival in patients with refractory liver metastases of colorectal cancer. Medicine (Baltimore) *95(14)*: e3338, 2016. PMID: 27057913. DOI: 10.1097/MD.0000000000003338

137 Yang RN, Yang SH, Chang CC, Chien CC, Pan S and Huang CJ: Upregulation of fecal cytokeratin 19 is associated with prognosis in older colorectal cancer patients. Genet Test Mol Biomarkers *14(5)*: 703-708, 2010. PMID: 20854102. DOI: 10.1089/gtmb.2010.0047

138 Ye M, He Y, Lin H, Yang S, Zhou Y, Zhou L, Zhong J, Lu G, Zheng J, Xue ZX and Cai ZZ: High expression of atonal homolog 8 predicts a poor clinical outcome in patients with colorectal cancer and contributes to tumor progression. Oncol Rep *37(5)*: 2955-2963, 2017. PMID: 28393252. DOI: 10.3892/or.2017.5554

139 Yeo SG, Kim DY, Chang HJ, Park JW, Oh JH, Kim BC, Baek JY, Kim SY and Kim TH: Reappraisal of pretreatment carcinoembryonic antigen in patients with rectal cancer receiving preoperative chemoradiotherapy. Tumori *99(1)*: 93-99, 2013. PMID: 23549007. DOI: 10.1700/1248.13795

140 Yu H, Son GM and Joh YG: The clinical significance of preoperative serum levels of carbohydrate antigen 19-9 in colorectal cancer. J Korean Surg Soc *84(4)*: 231-237, 2013. PMID: 23577318. DOI: 10.4174/jkss.2013.84.4.231

141 Zhan T, Gu J, Li M and Du C: Intermediate-fraction neoadjuvant radiotherapy for rectal cancer. Dis Colon Rectum *56(4)*: 422-432, 2013. PMID: 23478609. DOI: 10.1097/DCR.0b013e31828576c6

142 Zhang LN, Xiao W, OuYang PY, You K, Zeng ZF, Ding PR, Pan ZZ, Xu RH and Gao YH: The prognostic impact of preoperative blood monocyte count in pathological T3N0M0 rectal cancer without neoadjuvant chemoradiotherapy. Tumour Biol *36(10)*: 8213-8219, 2015. PMID: 25994571. DOI: 10.1007/s13277-015-3560-6

143 Zhang S, Gao F, Luo J and Yang J: Prognostic factors in survival of colorectal cancer patients with synchronous liver metastasis. Colorectal Dis *12(8)*: 754-761, 2010. PMID: 19508508. DOI: 10.1111/j.1463-1318.2009.01911.x

144 Zimmer R and Thomas P: Mutations in the carcinoembryonic antigen gene in colorectal cancer patients: implications on liver metastasis. Cancer Res *61(7)*: 2822-2826, 2001. PMID: 11306451.

145 Engstrand J, Nilsson H, Strömberg C, Jonas E and Freedman J: Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer *18(1)*: 78, 2018. PMID: 29334918. DOI: 10.1186/s12885-017-3925-x

146 Minhas A, Hendrickson J and Minhas SA: Frequency and risk factors for metastasis in newly diagnosed appendiceal carcinoma. Cureus *13(7)*: e16341, 2021. PMID: 34395124. DOI: 10.7759/cureus.16341

147 Sack TL, Gum JR, Low MG and Kim YS: Release of carcinoembryonic antigen from human colon cancer cells by phosphatidylinositol-specific phospholipase C. J Clin Invest *82(2)*: 586-593, 1988. PMID: 3042807. DOI: 10.1172/JCI113636

148 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ *372*: n71, 2021. PMID: 33782057. DOI: 10.1136/bmj.n71

Received June 13, 2022
Revised June 29, 2022
Accepted July 4, 2022