Research Square

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Difference in the performance of diagnosing colorectal liver metastasis between computed tomography and carcinoembryonic antigen

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Primary research

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Abstract

Background: The study was performed to compare the diagnostic roles of computed tomography (CT) and carcinoembryonic antigen (CEA) in colorectal liver metastasis (CRLM).

Methods: 255 patients with colorectal cancer (CRC) were enrolled. These patients were confirmed as CRLM by histopathological assay. CT scans of the liver were performed with a 64-slice CT system. Serum CEA levels were determined using a human circulating cancer biomarker magnetic bead panel. True positive (TP), false positive (FP), true negative (TN) and false negative (FN) were calculated for CT and CEA with histopathological assay as golden standard.

Results: 142 CRLM patients and 113 non-CRLM patients were confirmed in the study. There were no obvious differences in age, sex and Dukes stage between CRLM and non-CRLM patients (P 0.05). Diagnostic roles of CT and CEA on per-patient and per-lesion were analyzed. Detection sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CT on per-patient basis were 74.7%, 56.4%, 52.1%, and 77.9%, respectively. Sensitivity, specificity, PPV and NPV of CEA were 64.4%, 51.4%, 49.3%, and 67.3%. In the analysis on per-lesion basis, detection sensitivity, specificity, PPV, and NPV of CT were increased to 87.8%, 88.8%, 91.5%, and 84.1%, respectively. Detection sensitivity, specificity, PPV and NPV of CEA on per-lesion basis were 82.6%, 64.4%, 63.4%, and 83.2%.

Conclusion: CT exhibited better performances than CEA in diagnosis of CRLM on both of per-patient and per-lesion basis.

Background

Colorectal cancer (CRC) often metastasizes to other organs, among which liver is the most common site [1]. Fifteen to twenty-five percent cases with colorectal liver metastases (CRLM) are presented among CRC patients at primary diagnosis. About 15%-20% of CRC patients will develop liver metastases after resection surgery on primary tumor [2]. Detection of CRLM has important influence on treatment methods and prognosis of CRC patients. Specific information about the localization, number and size of metastasized liver lesions contributes to making decision on surgery, adjuvant therapy or palliative therapy [3, 4].

Tumor visualization is commonly performed with imaging techniques such as magnetic resonance imaging (MRI), ultrasonography and computed tomography (CT) [5]. Albrecht et al. (2014) reported that CT sensitivity and specificity were 63.55%-89.71% and 78.60%-94.41%, respectively. It also demonstrated that CT interpretation in detection of CRLM is less affected compared to MRI analysis [6]. A meta-analysis demonstrated that diagnostic sensitivity of CT was 74.4% and 83.6% on a per-patient basis and per-lesion basis, respectively. The detection accuracy of CT was lower than MRI and positron emission tomography (PET) [7].

Carcinoembryonic antigen (CEA), first described in 1965, is one of intracellular glycoprotein observed in 90% of CRC cases [8]. It serves as intercellular adhesion molecules that accelerate the aggregation of CRC cells [9, 10]. CEA, also named as CD66a and CEACAM5, is one of diagnostic biomarkers for many cancers [11–15]. For CRC and CRLM, CEA is the most commonly used biomarker. It is primarily applied to test recurrence of CRC rather than screening because of low sensitivity and specificity [16, 17]. However, this marker molecule is much more sensitive in diagnosis of lymph node metastases and CRLM than lung metastases and local recurrence [16–18].

Our study aimed to evaluate the diagnostic roles of CT and CEA in CRLM and compared their differences in diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Methods

This study was approved by the ethics committee of Southwest Hospital, Army Medical University. Written informed consent was obtained from all patients.

A total of 255 CRC patients from the hospital were enrolled. They were confirmed as primary CRC by histopathological assay. Among them, 142 patients suffered liver metastases and 113 patients did not. CRLM patients, synchronous or metachronous, were diagnosed by histopathological assay. The individuals with extra-hepatic metastasis were excluded from the study. The basic information of patients was showed in Table 1.

Table 1
Demographic data of all patients

Demographic data	Liver matastasis (n = 142)	No liver metastasis (n = 113)
Age, years	58.87 ± 10.35	56.57 ± 12.81
Sex (male/female, n)	86/56	71/42
Dukes stage		
	41	34
	53	48
	48	31
	0	0

CT

CT scans of the liver were performed with a 64-slice CT system (Somatom Sensation; Siemens, Erlangen, Germany). The following parameters were used in the measurement: CARE-Dose: on, 120 kV, up to 200 mA, rotation time 0.5 s, pitch 1.4, collimation, 0.6 mm, increment 2. The effective dose was about 8–

9 mSv. All patients were intravenously injected with 100 mL of iomeprol (Iomeron; Bracco) 300 mg Iodine/ml. The injection rate was 4 mL/s. After the images were obtained, all images were evaluated by Impax PACS workstation (Agfa, Mortsel, Belgium) with two Coronis monitors (1600 × 1200 pixels; Megapixels Diagnostic Display System; Barco, Kortijk, Belgium).

CEA measurement

Serum CEA levels were determined using a human circulating cancer biomarker magnetic bead panel (Merck Millipore, Billerica, MA, USA). The samples were measured in duplicates.

Statistics

All the analyses were completed in SPSS 18.0. The difference in average age between CRLM and non-CRLM patients was compared with independent t-test. X^2 test was used to analyze the differences in sex and Dukes stage. True positive (TP, a), false positive (FP, b), true negative (TN, d) and false negative (FN, c) were calculated for CT and CEA with histopathological assay as golden standard. Sensitivity = a/(a + c)*100%, specificity = d/(d + b)*100%, PPV = a/(a + b)*100%, NPV = d/(d + c)*100%. *P* value less than 0.05 indicated significant differences.

Results

Demographic data of subjects

The average age of patients with CRLM was 58.87 years, which exhibited no significant difference with that of non-CRLM patients (56.57 years, *P* 0.05). Male subjects accounted for a larger proportion than females in all patients. In addition, no obvious difference in Dukes stage between CRLM and non-CRLM patients was observed (*P* 0.05).

Diagnostic roles of CT and CEA in CRLM

Diagnostic roles of CT and CEA on per-patient and per-lesion basis were investigated (Table 2, 3). Diagnostic sensitivity and specificity of CT in CRLM on per-patient basis were 74.7% and 56.4%, higher than those of CEA (64.4% and 51.4%). PPV and NPV of CT were 52.1% and 77.9%, while PPV and NPV of CEA were 49.3% and 67.3%. 255 lesions were tested in the presented study. Diagnostic sensitivity and specificity of CT were 87.8% and 88.8%, which were higher than these values on per-patient basis. Diagnostic sensitivity and specificity of CEA were 82.6% and 64.4%. PPV and NPV of CT were 91.5% and 84.1%, while PPV and NPV of CEA were 63.4% and 83.2%. CT behaved better than CEA in diagnosis of CRLM.

Table 2
Overall diagnostic performance on per-patient basis

	CT		CEA	
	%	n	%	n
Sensitivity	74.7	74/99	65.4	70/107
Specificity	56.4	88/156	51.4	76/148
PPV	52.1	74/142	49.3	70/142
NPV	77.9	88/113	67.3	76/113

Table 3
Overall diagnostic performance on per-lesion basis

	CT		CEA	
	%	n	%	n
Sensitivity	87.8	130/148	82.6	90/109
Specificity	88.8	95/107	64.4	94/146
PPV	91.5	130/142	63.4	90/142
NPV	84.1	95/113	83.2	94/113

Discussion

CRC ranks third regarding cancer deaths in the world. For CRC patients, imaging of the liver is the traditional method to detect synchronous hepatic metastases [19, 20]. The detection of liver metastases occurred in CRC patients is crucial for treatment strategy and high detection sensitivity is also important.

Unenhanced ultrasound (US) technology on the liver shows a detection sensitivity of 50%-70% for synchronous liver metastases [21, 22]. However, US possess a limitation of low imaging contrast between liver parenchyma and liver lesions. Bipat et al. suggested that US should simply be used to differentiate patients with diffuse CRLM from patients with few metastases [23]. As for CRLM, the information about liver metastases, such as number, size, distribution location and volume of the lesions as well as volume of the rest should be grasped in detail before selecting surgical treatment [24]. Fortunately, CT is able to exactly complete this task. Until now, CT is the main diagnosis method for CRLM due to its high-resolution imaging and re-modified images, which makes the inspection of small metastases available. Meanwhile, the accurate measurement of volume and the location description of metastases by portal

venous anatomy and imaging hepatic arterial about normal and tumor liver by CT are both equally important for planning the surgical resection of CRLM [24]. The diagnostic sensitivity of contrast enhanced CT in liver metastases ranges from 68–85% [25–28].

In addition of these imaging modalities, tumor markers of type Ⅳcollagen (COLIV) and CEA were also used in the diagnosis of CRLM. Nyström et al. measured COLIV and CEA levels in CRLM patients and found that circulating COLIV level increased in 81% and CEA in 56% of CRLM patients at diagnosis. It also demonstrated that the diagnostic sensitivity of COLIV was lower than CEA [29]. Besides, Zhang et al. reported that serum CEA level was an independent prognostic predictor for CRLM [30]. Positron emission tomography (PET)/computed tomography (CT) was demonstrated to be superior to CEA in diagnosis of CRC and its recurrences [31].

Our study was performed to compare the diagnostic roles of CT and CEA in CRLM. On per-patient basis, CT showed better performance than CEA, exhibiting in sensitivity, specificity, PPV and NPV. On per-lesion basis, the diagnostic indexes of CT and CEA showed certain improvements, however, CT was still superior to CEA. The study firstly evaluated the difference in diagnostic accuracy between CT and CEA and the results were reliable and credible. However, several points must be noted in the analysis. Only 255 CRC patients were enrolled and the sample size was relatively small, hence, future larger-scale studies should be conducted to confirm the results. Moreover, more diagnostic modalities, such as MRI, PET/CT and contrast enhanced ultrasound (CEUS) should be considered, which will provide more accurate results about diagnosis methods of CRLM.

Conclusions

In a conclusion, CT was superior to CEA in diagnosis of CRLM. The results may contribute to the improvement in early diagnosis of CRLM and selection of surgical methods.

List Of Abbreviations

Computed tomography (CT)

Carcinoembryonic antigen (CEA)

Colorectal liver metastasis (CRLM).

Colorectal cancer (CRC)

True positive (TP)

False positive (FP)

True negative (TN)

False negative (FN)

Magnetic resonance imaging (MRI)

Positron emission tomography (PET)

Positive predictive value (PPV)

Negative predictive value (NPV)

Unenhanced ultrasound (US)

collagen (COLIV)

Contrast enhanced ultrasound (CEUS)

Declarations

Ethics approval and consent to participate

This study was supported by the Ethics Committee of Southwest Hospital, Army Medical University and also has been carried out in accordance with the World Medical Association Declaration of Helsinki.

The subjects had been informed the objective. Certainly, written consents were signed by every subject in this study.

Consent for publication

We obtaining permission from participants to publish their data.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

K.Z. and Z.W. design of the work; T.M. and Z.H. the acquisition, analysis, X.W. and Y.P. interpretation of data; Y.C. and Y.D. the creation of new software used in the work; Z.R. have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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References

1. Yoon SS, Tanabe KK: **Surgical treatment and other regional treatments for colorectal cancer liver metastases**. *The oncologist* 1999, **4**(3):197-208.
2. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM: **Epidemiology and management of liver metastases from colorectal cancer**. *Annals of surgery* 2006, **244**(2):254-259.
3. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH: **Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases**. *Annals of surgery* 1999, **230**(3):309-318; discussion 318-321.
4. Ruers T, Bleichrodt RP: **Treatment of liver metastases, an update on the possibilities and results**. *Eur J Cancer* 2002, **38**(7):1023-1033.
5. Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, Stoker J: **Colorectal liver metastases: CT, MR imaging, and PET for diagnosis–meta-analysis**. *Radiology* 2005, **237**(1):123-131.
6. Albrecht MH, Wichmann JL, Muller C, Schreckenbach T, Sakthibalan S, Hammerstingl R, Bechstein WO, Zangos S, Ackermann H, Vogl TJ: **Assessment of colorectal liver metastases using MRI and CT: impact of observer experience on diagnostic performance and inter-observer reproducibility with histopathological correlation**. *European journal of radiology* 2014, **83**(10):1752-1758.
7. Niekel MC, Bipat S, Stoker J: **Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment**. *Radiology* 2010, **257**(3):674-684.
8. Goldstein MJ, Mitchell EP: **Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer**. *Cancer investigation* 2005, **23**(4):338-351.
9. Duffy MJ, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, Nilsson O, Sturgeon C, Topolcan O: **Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines**. *Eur J Cancer* 2003, **39**(6):718-727.
10. Hanke B, Riedel C, Lampert S, Happich K, Martus P, Parsch H, Himmler B, Hohenberger W, Hahn EG, Wein A: **CEA and CA 19-9 measurement as a monitoring parameter in metastatic colorectal cancer (CRC) under palliative first-line chemotherapy with weekly 24-hour infusion of high-dose 5-fluorouracil (5-FU) and folinic acid (FA)**. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2001, **12**(2):221-226.
11. Rehena Z, Ghosh CK, Afroz F, Alam MB, Ferdousi S, Mahmuduzzaman M, Sultana T, Ahmed AN: **Comparison of Serum CA72-4 and CEA Levels in Patient with Endoscopically Suspected Gastric Carcinoma**. *Mymensingh medical journal : MMJ* 2015, **24**(3):542-549.
12. Thomas DS, Fourkala EO, Apostolidou S, Gunu R, Ryan A, Jacobs I, Menon U, Alderton W, Gentry-Maharaj A, Timms JF: **Evaluation of serum CEA, CYFRA21-1 and CA125 for the early detection of colorectal cancer using longitudinal preclinical samples**. *British journal of cancer* 2015, **113**(2):268-274.

13. Son SM, Han HS, An JY, Choe KH, Lee KM, Lee KH, Kim SS, Lee YM, Lee HC, Song HG *et al*: **Diagnostic performance of CD66c in lung adenocarcinoma-associated malignant pleural effusion: comparison with CEA, CA 19-9, and CYFRA 21-1**. *Pathology* 2015, **47**(2):123-129.
14. Yang AP, Liu J, Lei HY, Zhang QW, Zhao L, Yang GH: **CA72-4 combined with CEA, CA125 and CAl9-9 improves the sensitivity for the early diagnosis of gastric cancer**. *Clinica chimica acta; international journal of clinical chemistry* 2014, **437**:183-186.
15. Wang G, Qin Y, Zhang J, Zhao J, Liang Y, Zhang Z, Qin M, Sun Y: **Nipple discharge of CA15-3, CA125, CEA and TSGF as a new biomarker panel for breast cancer**. *International journal of molecular sciences* 2014, **15**(6):9546-9565.
16. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen C: **An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer**. *Jama* 1993, **270**(8):943-947.
17. Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, George S, Mant D: **Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial**. *Jama* 2014, **311**(3):263-270.
18. Tan E, Gouvas N, Nicholls RJ, Ziprin P, Xynos E, Tekkis PP: **Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer**. *Surgical oncology* 2009, **18**(1):15-24.
19. Wald C, Scheirey CD, Tran TM, Erbay N: **An update on imaging of colorectal cancer**. *The Surgical clinics of North America* 2006, **86**(4):819-847.
20. Gollub MJ, Schwartz LH, Akhurst T: **Update on colorectal cancer imaging**. *Radiologic clinics of North America* 2007, **45**(1):85-118.
21. Larsen LP, Rosenkilde M, Christensen H, Bang N, Bolvig L, Christiansen T, Laurberg S: **The value of contrast enhanced ultrasonography in detection of liver metastases from colorectal cancer: a prospective double-blinded study**. *European journal of radiology* 2007, **62**(2):302-307.
22. Piscaglia F, Corradi F, Mancini M, Giangregorio F, Tamberi S, Ugolini G, Cola B, Bazzocchi A, Righini R, Pini P *et al*: **Real time contrast enhanced ultrasonography in detection of liver metastases from gastrointestinal cancer**. *BMC cancer* 2007, **7**:171.
23. Scheele J, Stang R, Altendorf-Hofmann A, Paul M: **Resection of colorectal liver metastases**. *World journal of surgery* 1995, **19**(1):59-71.
24. Xu LH, Cai SJ, Cai GX, Peng WJ: **Imaging diagnosis of colorectal liver metastases**. *World journal of gastroenterology : WJG* 2011, **17**(42):4654-4659.
25. Ohlsson B, Nilsson J, Stenram U, Akerman M, Tranberg KG: **Percutaneous fine-needle aspiration cytology in the diagnosis and management of liver tumours**. *The British journal of surgery* 2002, **89**(6):757-762.
26. Valls C, Andia E, Sanchez A, Guma A, Figueras J, Torras J, Serrano T: **Hepatic metastases from colorectal cancer: preoperative detection and assessment of resectability with helical CT**. *Radiology* 2001, **218**(1):55-60.

27. Rappeport ED, Loft A: **Liver metastases from colorectal cancer: imaging with superparamagnetic iron oxide (SPIO)-enhanced MR imaging, computed tomography and positron emission tomography**. *Abdominal imaging* 2007, **32**(5):624-634.
28. Kim YK, Ko SW, Hwang SB, Kim CS, Yu HC: **Detection and characterization of liver metastases: 16-slice multidetector computed tomography versus superparamagnetic iron oxide-enhanced magnetic resonance imaging**. *European radiology* 2006, **16**(6):1337-1345.
29. Nystrom H, Tavelin B, Bjorklund M, Naredi P, Sund M: **Improved tumour marker sensitivity in detecting colorectal liver metastases by combined type IV collagen and CEA measurement**. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* 2015, **36**(12):9839-9847.
30. Zhang D, Yu M, Xu T, Xiong B: **Predictive value of serum CEA, CA19-9 and CA125 in diagnosis of colorectal liver metastasis in Chinese population**. *Hepato-gastroenterology* 2013, **60**(126):1297-1301.
31. Makis W, Kurzencwyg D, Hickeson M: **18F-FDG PET/CT superior to serum CEA in detection of colorectal cancer and its recurrence**. *Clinical imaging* 2013, **37**(6):1094-1097.