Selection of colon cancer patients for neoadjuvant chemotherapy based on optimised preoperative MDCT A prospective multi-observer radiologic-pathologic agreement study

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Purpose

- To evaluate the accuracy of preoperative MDCT in the differentiation between locally advanced colon cancer (LACC) and non-locally advanced colon cancer (NLACC).

Background and relevance of the topic:

The current treatment of potentially resectable locally advanced colon cancer (LACC), including high risk stage II or stage III disease is surgery followed by adjuvant chemotherapy. Given proven efficacy in the adjuvant setting, benefits of preoperative therapy are also expected [1]. Furthermore, neoadjuvant chemotherapy and radiotherapy are substantially more effective than similar postoperative therapy in oesophageal, gastric, and rectal cancer [2, 3].

A phase III clinical trial, the FOxTROT Collaborative Group Trial [4], is now in course evaluating the benefits of neoadjuvant chemotherapy (NACT) in potentially resectable LACC.

- LACC includes tumours staged pre-operatively as T4 or T3 with #5mm invasion beyond the muscular layer.
- Non locally advanced colon cancer (NLACC) includes tumours in stages T1, T2, T3 with <5mm invasion beyond the muscular layer.

Pilot study results suggested that:

- NACT in potentially resectable LACC is likely to prove superiority compared to standard treatment.
- Patients can be appropriately selected for neoadjuvant chemotherapy with CT scanning.

The value of MDCT in CC staging has already been covered by several studies. However, if NACT proves to have a positive impact in the survival of patients with potentially resectable LACC, the distinction between NLACC and LACC (based on the invasion <5mm or #5mm beyond the *muscularis* layer) may become the most relevant feature to be determined preoperatively [4].

Methods and materials

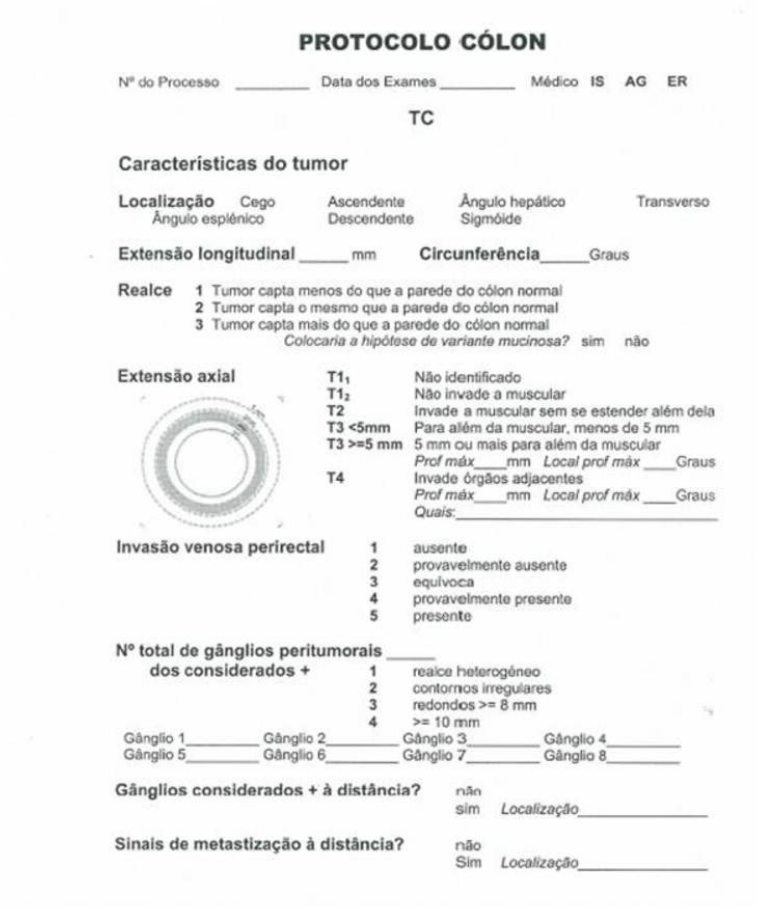
Observational, cross-sectional, prospective study.

- All patients with colon cancer referred to our Department for preoperative staging between the 1st of October 2013 and the 6th of August 2014 were included.
- Contrast-enhanced MCDT was performed with multiplanar reconstructions.
- Retrograde distention of the colon was achieved with water or air.
- Independent reading was performed by 4 radiologists, with 3, 6, 15 and 20 years of experience in gastrointestinal imaging.
- Relevant data was recorded in a specifically elaborated formulary (Fig. 1), with emphasis in local staging (Fig. 2).

After surgery:

- Specimen analysis was performed by a single pathologist with 12 years of experience in gastrointestinal pathology.
- Radiologic-pathologic agreement was assessed (Fig. 3-8) and sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Images for this section:



PROTOCOLO CÓLON

Nº do Processo _____ Data dos Exames _____ Médico IS AG ER

TC

Características do tumor

Localização Cego Ascendente Ângulo hepático Transverso
Ângulo esplénico Descendente Sigmóide

Extensão longitudinal _____ mm **Circunferência**_____Graus

Realce 1 Tumor capta menos do que a parede do cólon normal
2 Tumor capta o mesmo que a parede do cólon normal
3 Tumor capta mais do que a parede do cólon normal
Colocaria a hipótese de variante mucinosa? sim não

Extensão axial

T1₁ Não identificado
T1₂ Não invade a muscular
T2 Invade a muscular sem se estender além dela
T3 <5mm Para além da muscular, menos de 5 mm
T3 >=5 mm 5 mm ou mais para além da muscular
*Prof máx*____mm *Local prof máx* ____Graus
T4 Invade órgãos adjacentes
*Prof máx*____mm *Local prof máx* ____Graus
*Quais:*_____

Invasão venosa perirectal
1 ausente
2 provavelmente ausente
3 equívoca
4 provavelmente presente
5 presente

Nº total de gânglios peritumorais _____
dos considerados +
1 realce heterogéneo
2 contornos irregulares
3 redondos >= 8 mm
4 >= 10 mm

Gânglio 1_____ Gânglio 2_____ Gânglio 3_____ Gânglio 4_____
Gânglio 5_____ Gânglio 6_____ Gânglio 7_____ Gânglio 8_____

Gânglios considerados + à distância? não
sim *Localização*_____

Sinais de metastização à distância? não
Sim *Localização*_____

Fig. 1: Information sheet to be filled by each one of the 4 radiologists. It contains information on the localization of the tumour, degree of enhancement, local staging, signs of venous and lymph node invasion and distant metastasis.

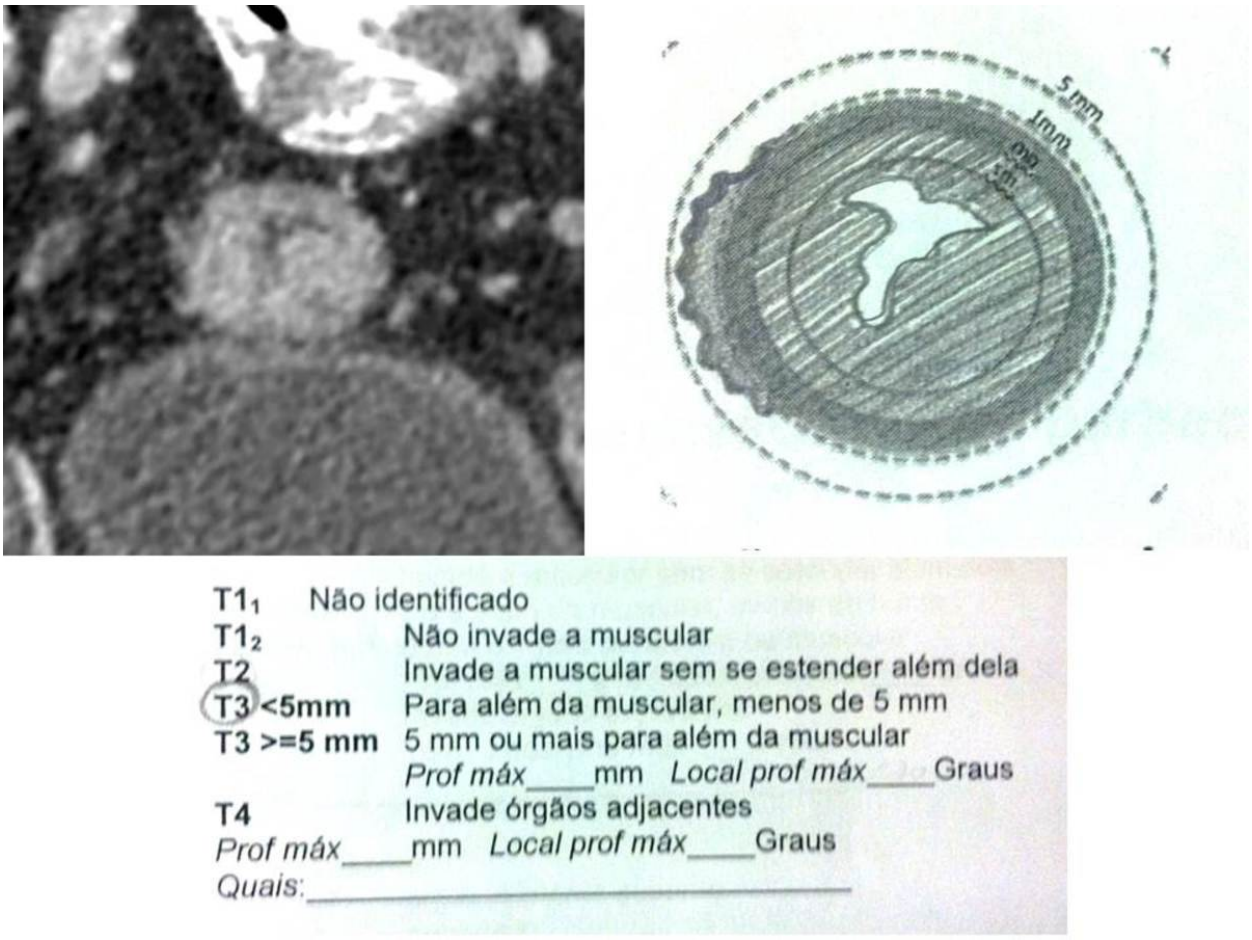


Fig. 2: Example of the local staging section. The radiologist examines the CT and makes a graphic representation of the tumour, showing the deepest infiltration of the colon wall. The circular lines on the graphic represent the mucosal layer and the muscularis propria. An additional line corresponding to 5mm distance from the muscularis is also represented. In the case shown, the tumour was staged as a T3 with less than 5mm invasion beyond the muscularis propria, and thus, as a NLACC.

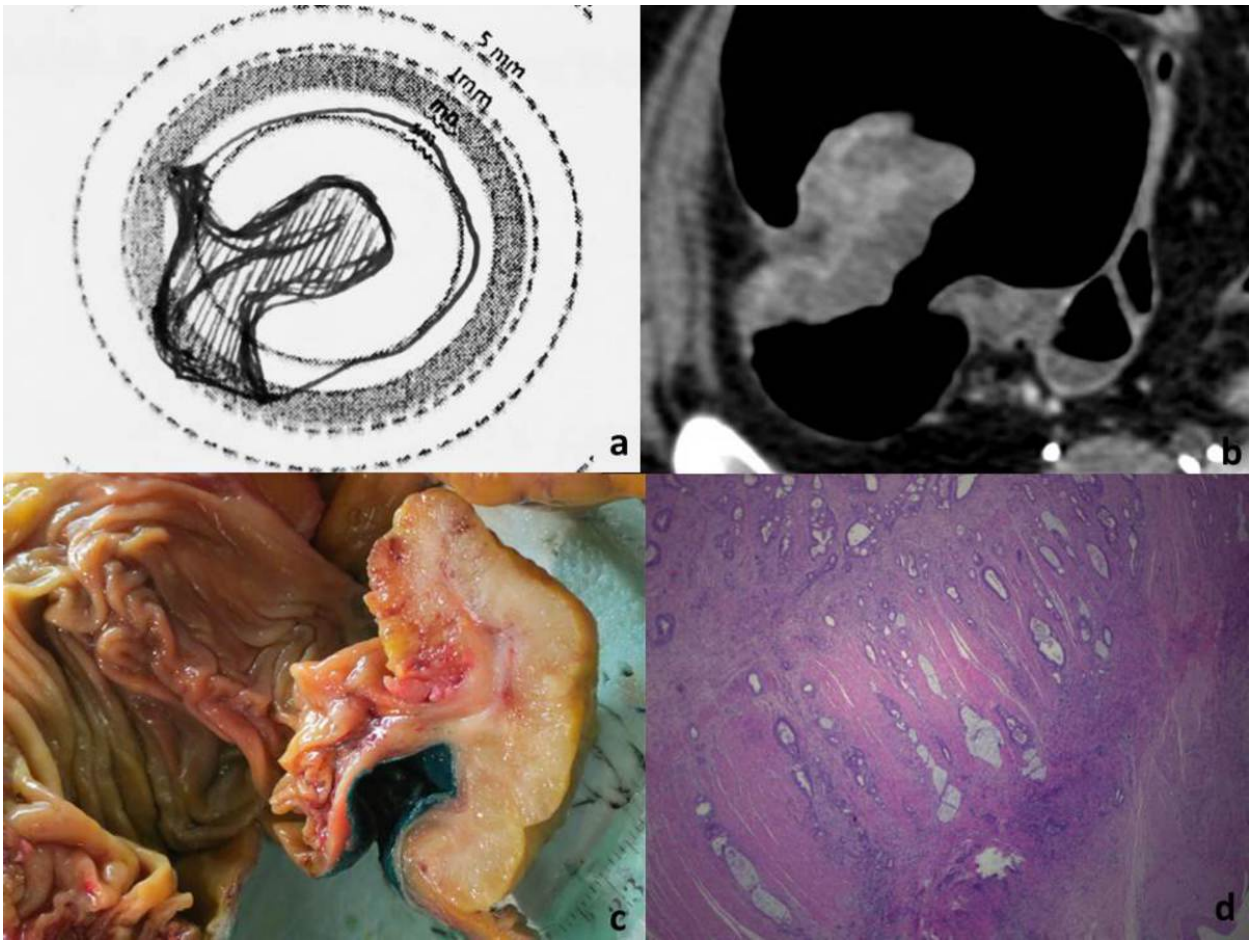


Fig. 3: Example of a T3 tumour with less than 5mm invasion beyond the muscular layer. Graphic representation made by the radiologist (a) and the corresponding MDCT axial section (b), gross pathology photography (c) and histology - H&E 25x (d) are shown.

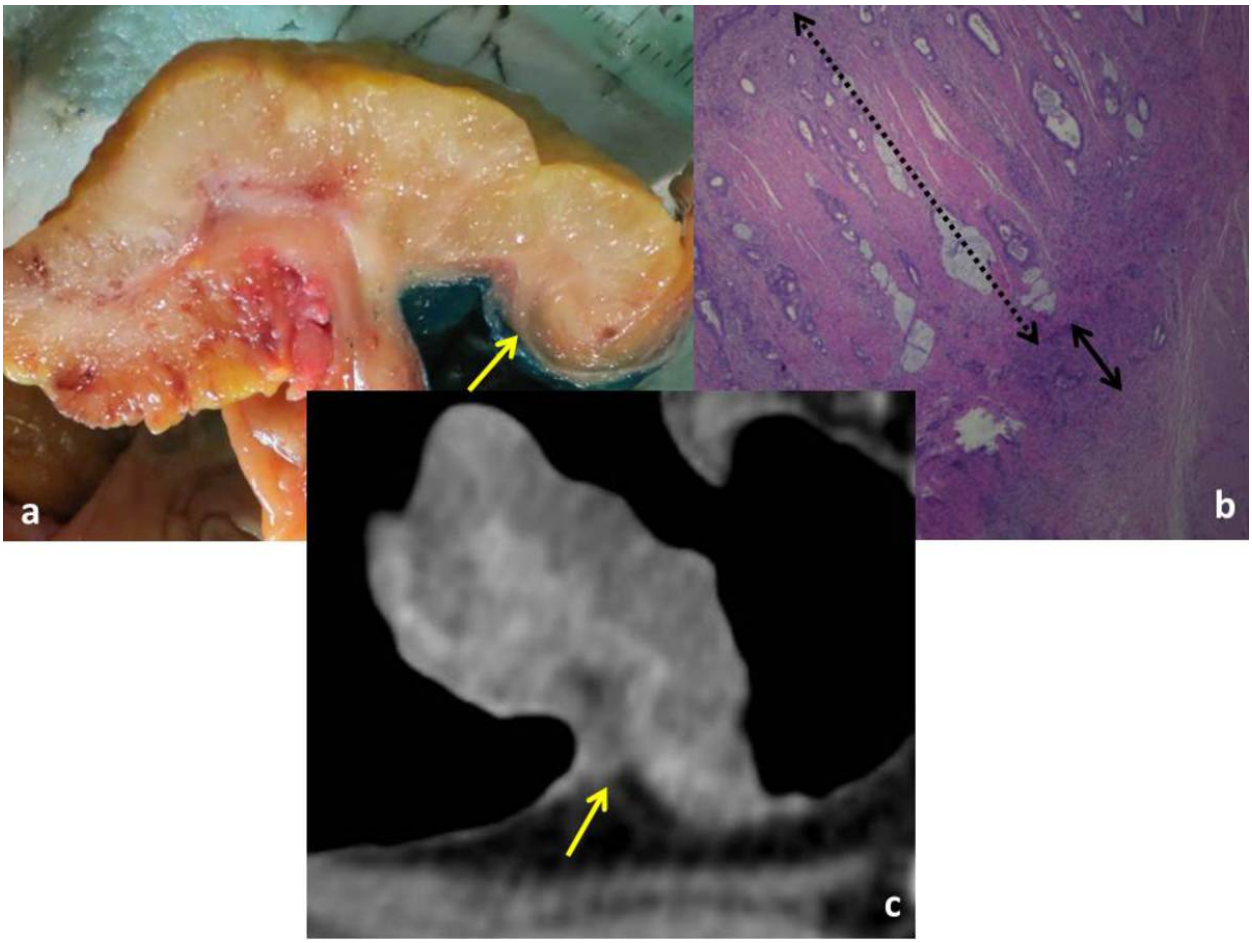


Fig. 4: Detailed analysis of the depth of invasion of the tumour shown in the previous figure. Gross pathology (a) is suspicious for tumour invasion of the muscular layer (yellow arrow). Histology - H&E 25x (b) confirmed that the muscular layer is infiltrated by tumour cells (dashed black arrow), some of them showing glandular differentiation. The invasion beyond the muscular layer is less than 5mm (double black arrow). In the MDCT (c) the invasion could be suspected in the pedicle of the polyp (yellow arrow).This is a T3 - NLACC.

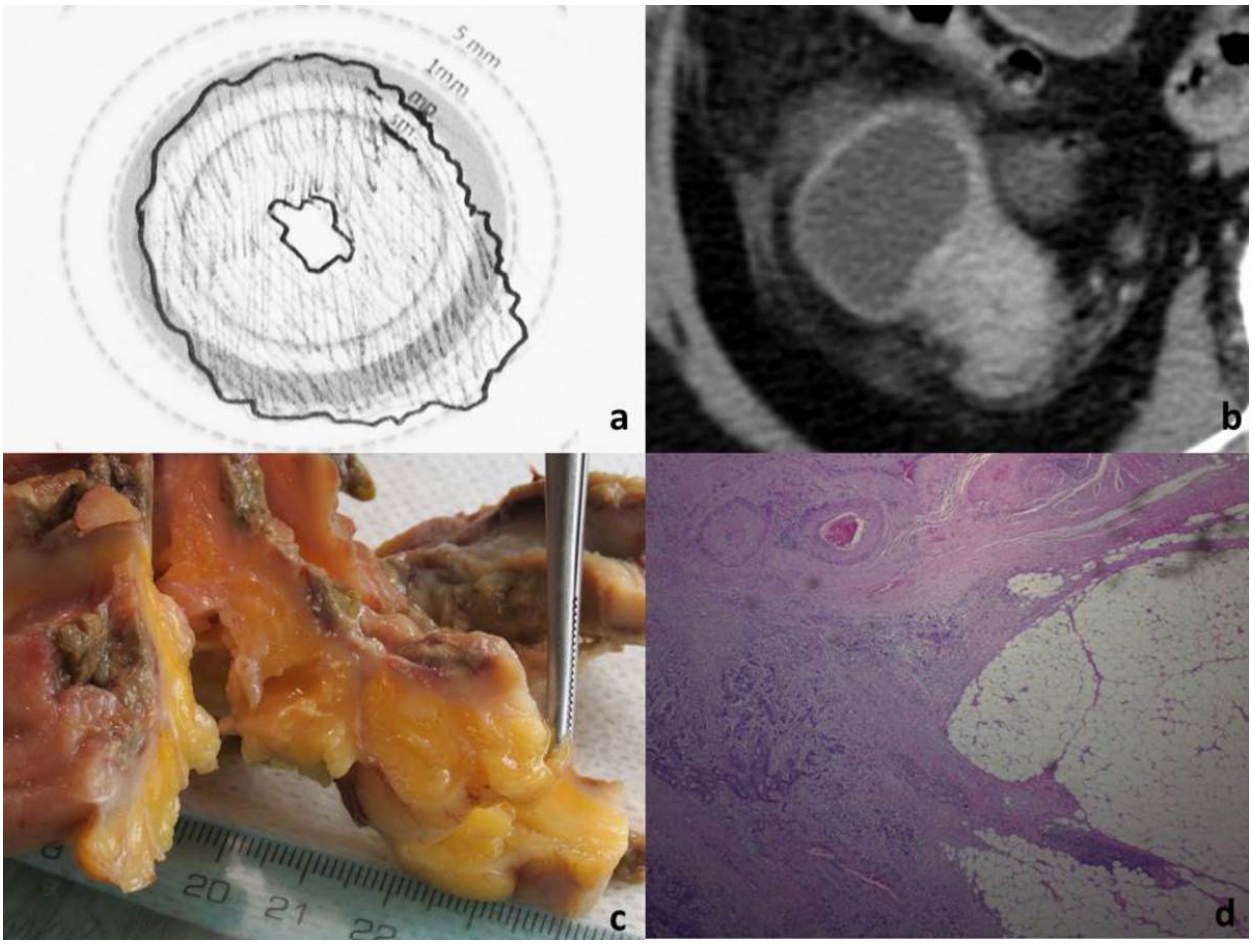


Fig. 5: Example of a T3 tumour with more than 5mm invasion beyond the muscular layer. Graphic representation made by the radiologist (a) and the corresponding MDCT axial section (b), gross pathology photography (c) and histology - H&E 25x (d) are shown.

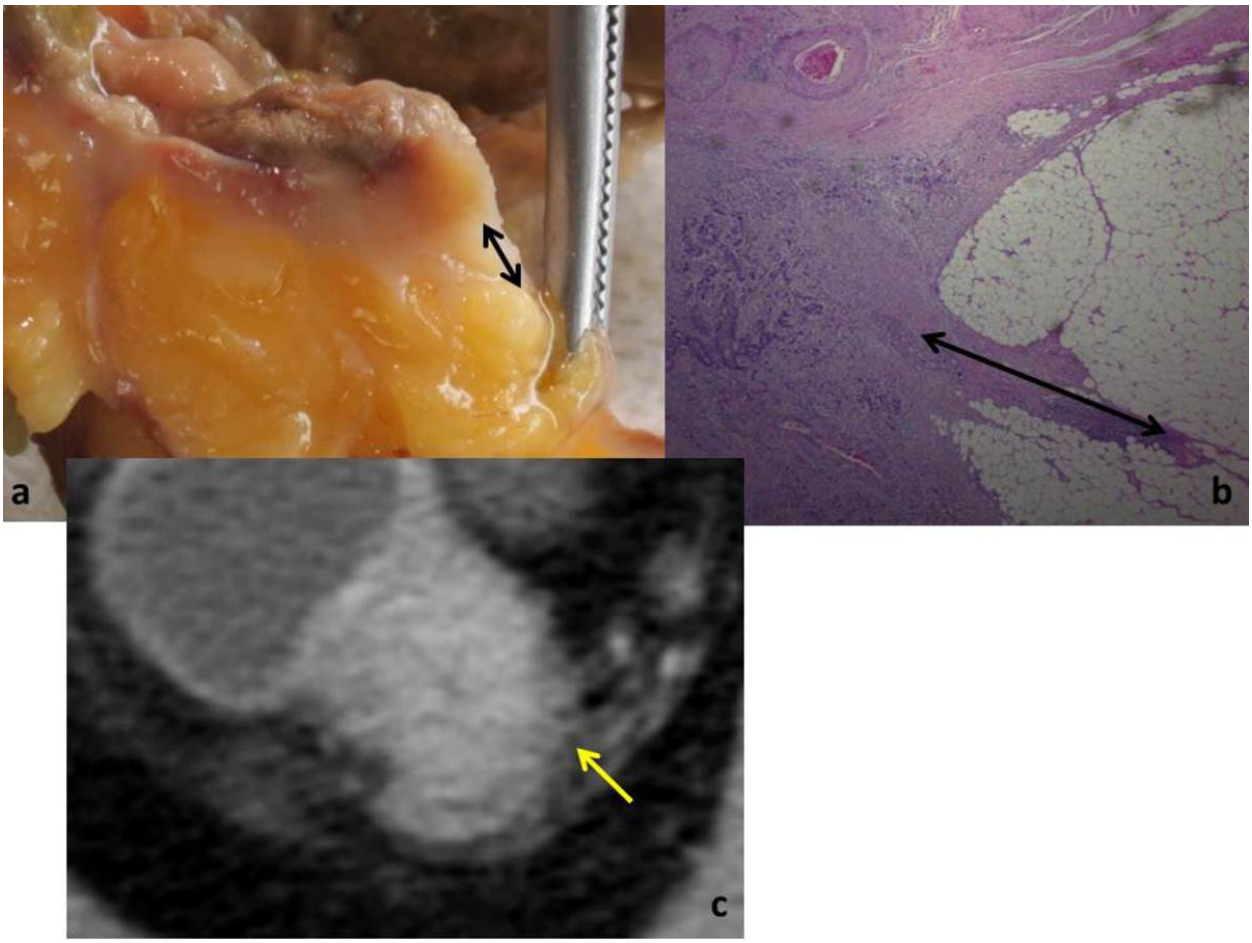


Fig. 6: Detailed analysis of the depth of invasion of the tumour shown in the previous figure. Gross pathology (a) shows that the tumour extends beyond the muscular layer, infiltrating adjacent fat (short double arrow). Histology - H&E 25x (b) confirmed that the invasion beyond the muscular layer is >5mm (long double arrow). MDCT (c) image was suspicious for invasion beyond the muscular layer (yellow arrow). Although staged as a T3, this tumour is considered a LACC.

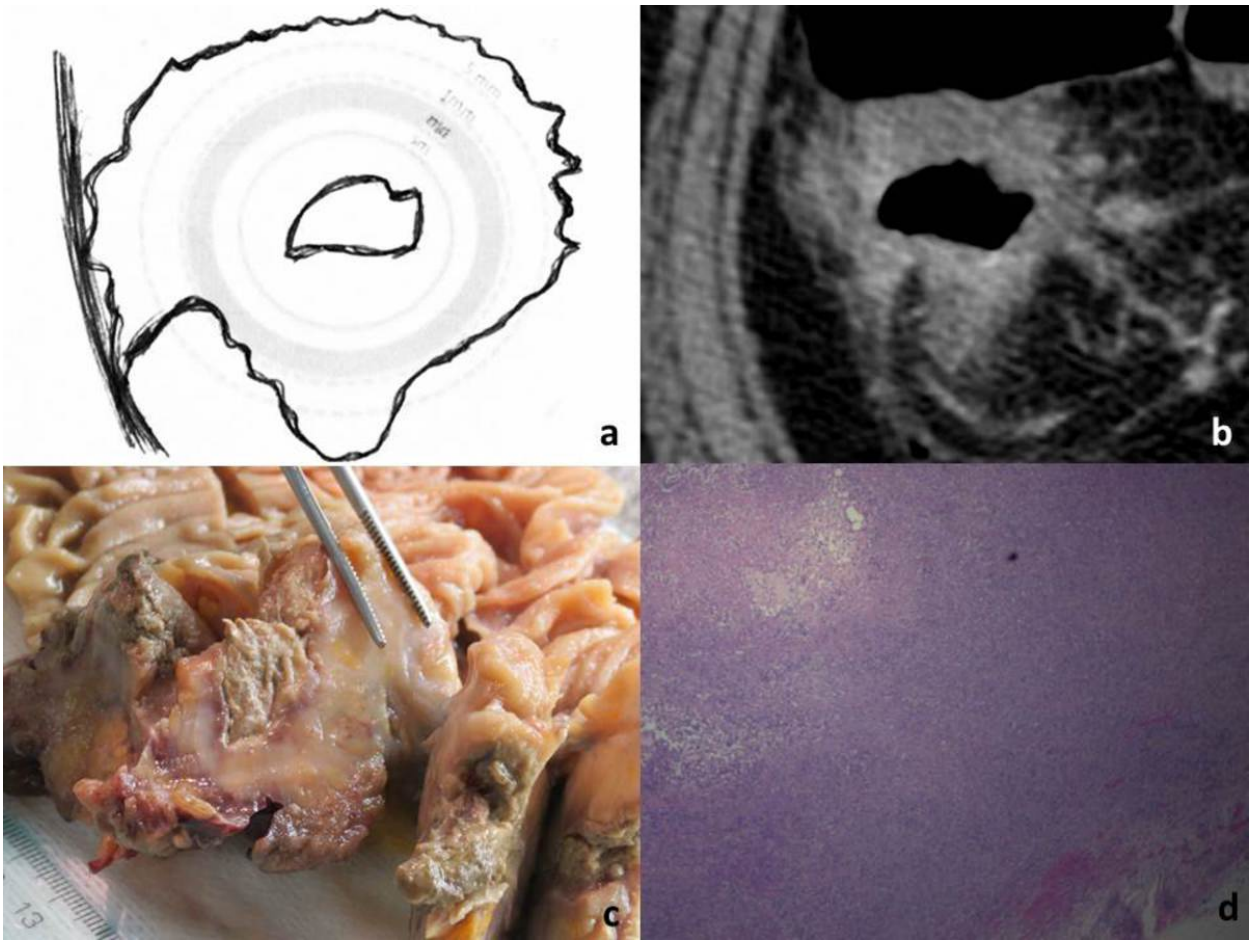


Fig. 7: Example of a T4 tumour with extension beyond the serosa. Graphic representation made by the radiologist (a) and the corresponding MDCT axial section (b), gross pathology photography (c) and histology - H&E 25x (d) are shown.

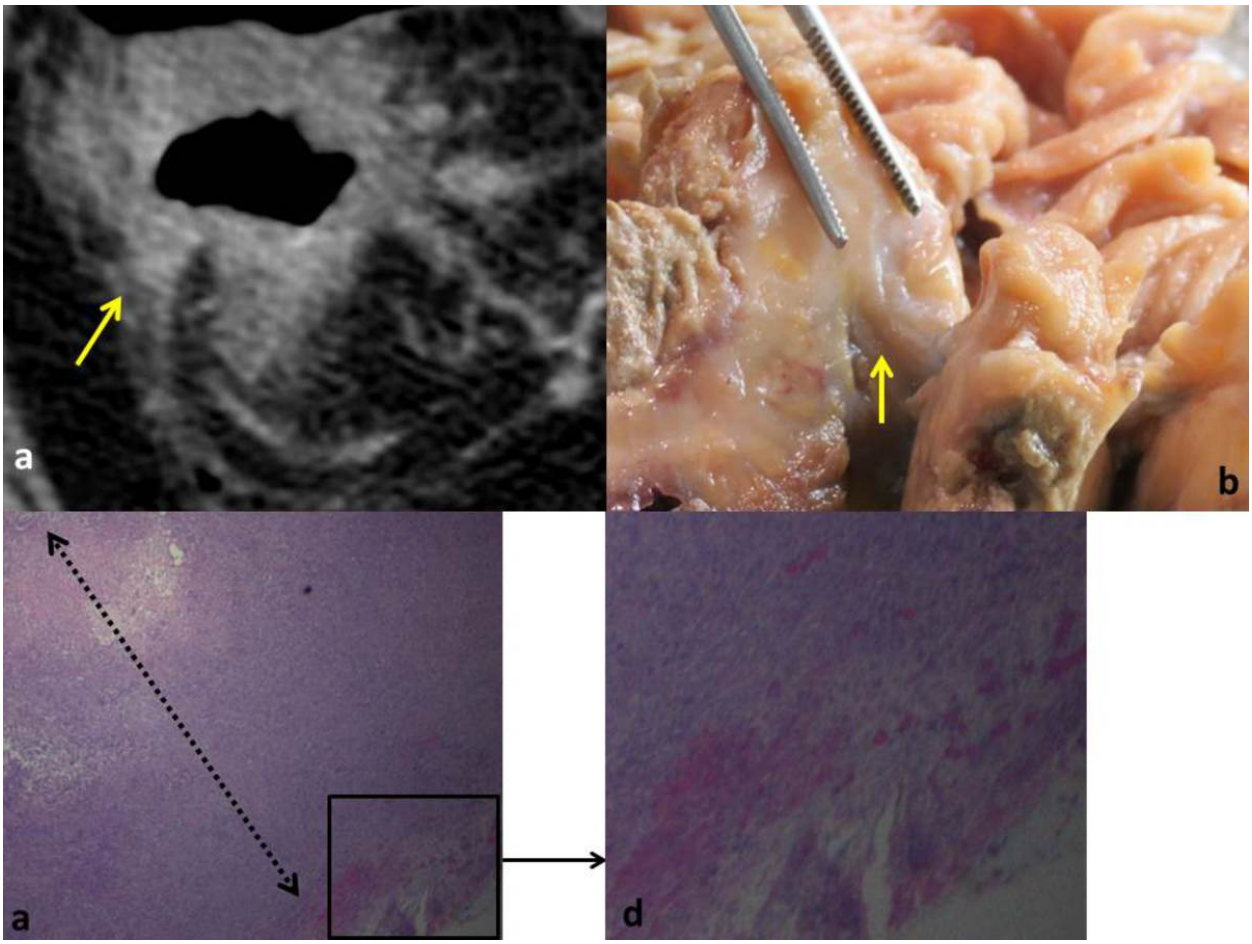


Fig. 8: Detailed analysis of the depth of invasion of the tumour shown in the previous figure. MDCT (a) and gross pathology (b) are suspicious for a T4 tumour, with peritoneal invasion (yellow arrows). Histology - H&E 25x (c) and amplified image (d) confirmed that the tumour cells infiltrated the full thickness of the colon wall (double dashed arrow), extending through the serosa (d). This is a T4a - LACC.

Results

We studied a total of 48 consecutive patients.

- 26 males and 22 females
- Median age: 74 years (range 45 to 89)
- Median time to surgery: 30,5 days (range 1 to 117 days)

Regarding the differentiation between LACC and NLACC with MDCT, we obtained:

- S: 0,64-0,82
- E: 0,84-0,92
- PPV: 0,5-0,7
- NPV: 0,88-0,97
- **Accuracy: 0,75-0,88**

Mean agreement between observers was 0,88 (SD:0,17) per patient.

Conclusion

Our study suggests that:

- Optimized MDCT is a specific, accurate and reproducible method for distinction between LACC and NLACC.
- There is a minimal risk of overtreatment of low-risk patient

Other studies have also shown a good accuracy of MDCT in CC staging:

1. A metha-analysis [5] published on this topic concluded that preoperative CT can be used to accurately distinguish between tumours confined to the bowel wall and those invading beyond the *muscularis* layer (differentiation between T1-T2 versus T3-T4):

- S: 86%
- E: 78%

2. Nørgaard A et al. also evaluated MDCT performance in the differentiation between LACC and NLACC:

- T staging accuracy: 69%
- 7% overstaged / 24% understaged

- **Identification of LACC was 73% accurate compared with histology (**S=70%; E=78%; PPV=81%; NPV=66%)

Study	Accuracy	S	E	PPV	NPV
Rosado E	**75-88%**	64%-82%	84%-92%	50%-70%	88%-97%
Nørgaard A	**73%**	70%	78%	81%	66%

Comparison between Nørgaard A. study and ours reveal a very similar overall accuracy for MDCT. Both studies emphasise that:

- **Optimized MDCT seems to be an accurate method for selection of colon cancer patients who may benefit from NACT.**

Personal information

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