

CT colonography for the detection of nonpolypoid colorectal lesions

A prospective series



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AIM: To determine the diagnostic accuracy of CT-colonography (CTC) for colorectal nonpolypoid lesions.

MATERIALS AND METHODS. In the period 2010-2011, 51 out of 454 patients undergoing CTC received also optical colonoscopy (OC). Three human readers with high, intermediate and low expertise interpreted the images. Flat lesions were defined as 3 mm or less in height; laterally spreading type (LST) lesions were defined as nonpolypoid lesions with more than 10 mm lateral diameter.

RESULTS: A total of 75 nonpolypoid colorectal lesions were identified in 21 patients: 43 type II-A low-grade adenomas, 2 type II-c Tis adenocarcinomas, 2 LST Tis adenocarcinomas, 24 nonadenomatous (hyperplastic) lesions and 4 LST infiltrating tumors (T1N0M0 in 2 cases and T2N0M0 in 2 cases). Per-lesion sensitivity and NPV were 44% and 80.5%, while per-patient sensitivity, specificity, PPV, NPV and accuracy were 80.9%, 93.7%, 89.5%, 88.2%, 88.7%. The readers with high and intermediate experience yielded significantly better diagnostic performances than reader with low experience ($p = 0.072$ and $p = 0.030$). All the infiltrating carcinomas and 75% of Tis carcinomas were detected by all the readers.

CONCLUSION. CTC showed a low per-lesion and an high per-patient diagnostic accuracy for all nonpolypoid colorectal lesions, but an high ability to detect nonpolypoid colorectal carcinomas. Diagnostic performances are strictly related to the reader experience.

KEY WORDS: Adenoma, Colon cancer, Colonoscopy CT colonography, Non polypoid lesions, Screening

Introduction

CT colonography (CTC) is increasingly employed in the setting of colorectal cancer screening¹, as well as in a number of clinical situations such as incomplete optical colonoscopy (OC), elderly and frail patients unfit for

OC, asymptomatic diverticular disease, tumor mapping before laparoscopic surgery and deep pelvic endometriosis². The American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology approved CTC for colorectal cancer screening³.

However, while major clinical trials⁴⁻⁶ reported an high diagnostic performance for cancer and polyps, detection of flat lesions is challenging⁷⁻¹⁰. From the recent Paris endoscopic classification¹¹ a neoplastic lesion is considered superficial when the depth of penetration in the colorectal wall is not more than into the submucosa; superficial lesions may be polypoid or nonpolypoid

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according to their height, measured in comparison with the height of the closed jaws of biopsy forceps (2.5 mm). Lesions protruding more than 2.5 mm are classified as polypoid, whereas those protruding below this level are classified as nonpolypoid. Nonpolypoid adenomas may represent precursors of cancer^{12,13} and may also bear a greater risk for malignancy compared with polypoid lesions, with particular reference to the so-called “serrated” adenomas^{13,14}.

The diagnostic performance of CTC for nonpolypoid lesions is not yet well-established^{7-10,15-18}. Differences in definition of nonpolypoid lesion (a lesion height less than half the greatest lesion diameter¹³ versus a maximum height of 2¹⁹, 2.5 or 3 mm), in the examination of reference (pathology versus optical colonoscopy), in the technical performance of CTC (bowel preparation, fecal tagging, computer-aided detection) hamper a definitive evaluation.

The aim of this study was to evaluate the diagnostic performances of CTC for nonpolypoid lesion, from a monocentric prospective recent series from a Radiological Department with long-standing specific expertise in this field.

Materials and Methods

The period analysis was September 2010-September 2011; all the patients undergoing CTC in the 1st Department of Radiology of Brescia Civil Hospital (total number, 454), which is a tertiary referral center, were screened for having been submitted to optical colonoscopy too in the 3 months before or after the CTC. Fifty-one patients were identified, which represent the main study group of this paper. There was no indication to each examen exclusively for research purpose; thus, only clinical indications dictated the procedure. Patients were formally enrolled before OC, even they have undergone the CTC before.

All the CTCs were performed with a unique standardized method: low-residue diet for 3 days, semifluid diet the evening before, 50 mL of hydrosoluble iodine agents (Gastrografin®, meglumine diatrizoate, Bayer Schering Pharma AG) diluted in 1000 mL water in the morning, not less than 6 hours in advance. N-butylbromure joscina (Buscopan®) was administered i.v. immediately before the examination. Carbon dioxide colonic distention was performed with an automated insufflator and a small rectal catheter with retention balloon (PROTO-CO₂L colon insufflator, E-Z-EM). Both supine and prone scans were obtained using a 64-MDCT scanner (Brilliance™ CT, Philips). IV contrast injection was performed only when requested, for example for staging purpose. All the scans were obtained with low-dose protocol: kv: 120, mAs = 50 or less and “iDose” (iterative reconstruction technique that modulates and further reduces the dose) on. Other parameters of CTC were:

acquisition slice 1mm, reconstruction 0,75mm, beam collimation, 64 × 0.75 mm; beam pitch, 1; gantry rotation time, 0.5 second. Cases were interpreted by 3 radiologists with different experience in CTC: an expert reader (reader 1), with more than 1000 previous examination, an intermediate reader (reader 2) with about 200 previous CTC and almost 15% of positive cases, and a novice low-experience reader (reader 3), which was in his learning curve of CTC. Post-processing of axial images was performed by the three readers on the same workstation (Extended Brilliance™ workspace, Philips). The interpretation was performed in the same way too: all the three radiologists usually performed CTC with primary 3D endoluminal fly-through antegrade and retrograde navigations, and 2D problem solving. Maximal lesion diameter and height were measured on the 2D multiplanar images²⁰. Extracolonic incidental findings were also recorded.

OC was performed by an experienced board-certified team; due to the design of this study, specifically aimed to the recognition of nonpolypoid colorectal lesions, all the available technical tools were employed, such as electronic chromoendoscopy, selective chromoendoscopy with indigo carmine and image magnification when needed; all the lesions, irrespectively of the diameter, were resected, by biopsy forceps, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) or with surgical resection.

Patients whose CTC and/or OC was sub-optimal because of inadequate bowel cleansing (Boston Preparation Scale ≤ 6) and/or inadequate bowel distention, or impossibility to perform cecal intubation, were excluded.

Lesion matching between CTC and OC was performed in consensus by the more experienced radiologist (GCM) and gastroenterologists (GLB & GM). Lesion matching was performed by comparing the segmental location, lesion size, morphology and location with respect to other easily recognizable structures. Lesions that fulfilled the following criteria for nonpolypoid colorectal lesions were considered: 3 mm or less in height at both CTC and OC for the main group analysis, and > 10 mm in diameter non polypoid lesions (LST, laterally spreading type), for a subgroup analysis.

The characteristics of all the resected nonpolypoid lesions, including histopathology, size, OC morphology according to the Paris classification¹¹, and the depth of mural extension in cancerous lesions, were recorded. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CTC was calculated for each reader, having as reference examination the OC. The diagnostic performance of the 3 readers was compared using Fisher's exact test. Data were interpreted per-lesion and per-patient. Analysis per-lesion clearly was performed accounting for true positive, false positive and false negative lesions only (no true negative cases were recorded), thus only sensitivity and positive predictive value were calculated. ROC curves were calculated.

Statistical analysis was carried out by using Microsoft Excel and SPSS version 18.0 for Windows. A p value of less than 0.05 was considered to be statistically significant.

Results

Overall, the patients who underwent both adequate CTC and complete CO were 51. A total of 21 patients (12 men and 9 women; mean age, 62.4 ± 12.1 years) with nonpolypoid colorectal lesions were finally included in this study. In all but 2 patients, the interval between CTC and colonoscopy was less than 2 months. Five of the 21 patients were referred for preoperative CTC with the aim of staging and/or localization of colorectal cancer in 3 cases, 1 diverticular disease and 1 caecal lipoma (in 2 cases non polypoid lesions were not resected during OC because they were localized in the segment of colon that would be subsequently surgically resected),

while the remaining 16 patients were firstly studied by CTC (the examination request was for screening in 7 cases, for abdominal complaints in 7 cases and for surveillance after cancer resection in 2 case) and subsequently underwent OC with the aim of removing 13 polypoid and 9 nonpolypoid lesions.

Overall, 75 nonpolypoid lesions were detected and removed by OC or by a subsequent surgical colon resection; the median number of lesion per patient was 2, because 2 patients had multiple lesions (18 in one case and 21 in the other one). Mean diameter was 4.1 mm (range, 3-17 mm). Pathological examination showed 43 Paris classification type II-A low-grade adenomas, 2 Paris classification type II-c Tis adenocarcinomas, 2 LST Tis adenocarcinomas, 24 nonadenomatous lesions (hyperplastic lesions) and 4 LST infiltrating tumors which staging was T1N0M0 in 2 cases and T2N0M0 in 2 cases. Reader 1 recognized 33 out of 75 lesions, and 8 more lesions which finally proved to be false positive on OC. The corresponding values for readers 2 and 3 were 27.8 and 21.3. Diagnostic performances in per-lesion analysis are reported in Table I. As expressed in material and methods, only sensitivity and PPV are Table II shows the per patient diagnostic performance; true negative were those patients in which both OC and CTC showed no lesions with morphological characteristics of nonpolypoid lesion. The sensitivity of the human readers for all nonpolypoid lesions (17/21, 16/21 and 12/21) in per-patient analysis was significantly higher than that for per-lesion analysis (33/75, 27/75, 21/75) ($p = 0.043$). However, sensitivity is not really so relevant, as it refers to almost 1 only lesion, while most patients had 2 lesions or more. Negative predictive values are upmost important from a clinical point of view, as those patients were really free from nonpolypoid lesions.

Figure 1 shows the ROC curves for the 3 readers with different specific experience; the difference in diagnostic performances was significant for reader 1 vs reader 3 ($p=0.072$) and reader 2 versus reader 3 ($p=0.030$).

Finally, extra-colonic pathological findings were detected in 18 patients out of 51, and specifically 13 kidney or gallbladder stones, 2 aortic or iliac aneurysms, 2 inci-

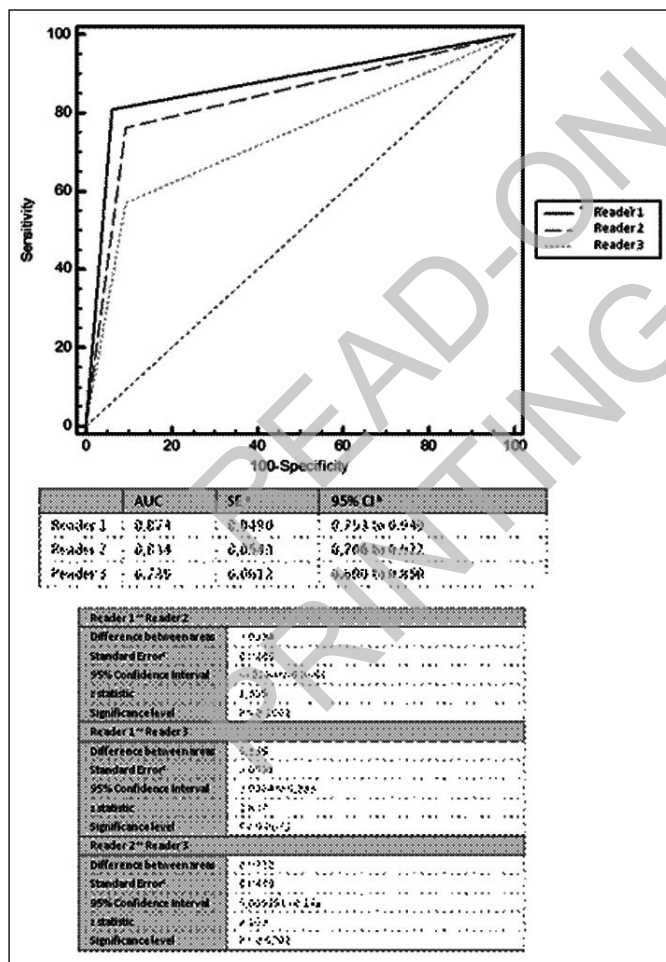


Fig. 1: The ROC curves of the 3 readers; the difference between the curves was significant for reader 1 vs reader 3 and reader 2 versus reader 3.

TABLE I - Diagnostic performances of 3 readers with a different specific expertise, considering per-lesion data: reader 1 had more than 1000 CTC, reader 2 about 200 CTC and reader 3 was in its learning curve.

	Reader 1	Reader 2	Reader 3
True positive	33	27	21
False positive	8	8	3
False negative	42	48	54
Sensitivity	44%	36%	28%
PPV	80.49%	77.14%	87.50%

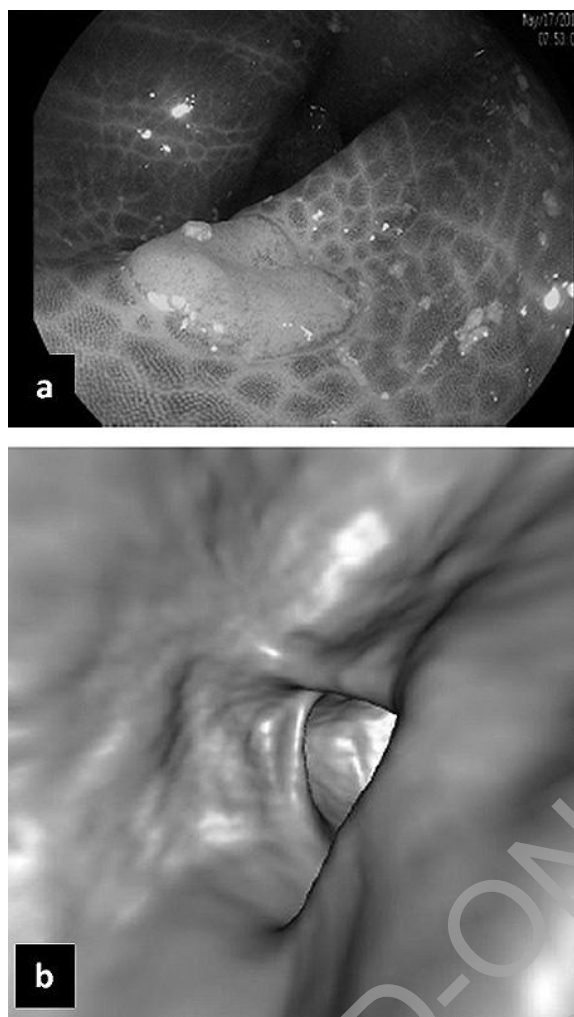


Fig. 2: CTC False negative: a 0-IIa lesion in a condition of melanosis coli (a) unidentified in the 3D image fly-through by all three readers with different CTC experience (b). 2D evaluation too didn't show this lesion.

sional haernia, 1 metachronous metastatic disease to liver and lung.

Examples of nonpolypoid adenomatous lesions detected or unrecognized in CTC are shown in Figures 2 and 3.

Discussion

There is considerable debate in the recent literature about the diagnostic accuracy of CTC in the detection of flat lesions of the colon and rectum. This paper aims to determine the actual diagnostic ability of CTC in a monocentric series which is homogeneous, recent, short-term, and comes from a center with an high volume and a long-standing reading experience of CTC.

Before interpreting the data, two methodological considerations should be done: first, the definition of flat lesion is crucial. From long time the widely shared def-

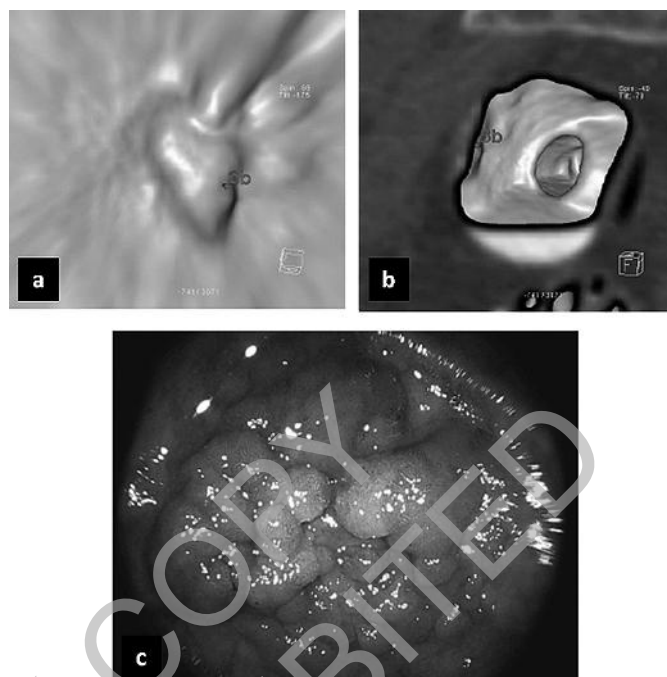


Fig. 3: CTC True positive: a slightly elevated 0-IIa lesion detected at the insertion of a sigmoidal plica and marked with "3b" by the radiologist in the 3D image fly-through (a) and in the 2D axial image (b). Optical colonoscopy confirmed the CTC finding (c).

inition was a lesion having a height less than half the diameter, but recently most Authors proposed to exclude large lesions which, while having no polypoid morphology, are easily identifiable by CTC for their dimensions⁸, and consider only the lesions whose height is lower than the biopsy forceps at OC. However this definition, which is certainly valid from a theoretical point of view, has some limitations, because there is no agreement upon the precise cut-off: 2, 2.5 or 3 mm? Moreover, the endoscopic measurement presents a considerable degree of variability, due to the dynamic conditions and different distension in which it can be carried out; finally, most of the lesions of this size have an actually very low chance to be advanced lesions, to the point that their identification does not necessarily improve the patients prognosis. The second consideration refers to the choice of the reference method: although the OC can be considered the gold-standard diagnostic for flat lesions of the colon, it is well known that in daily clinical practice an imperfect bowel cleansing does not allow a complete visualization of the mucosa of the entire colon in a significant proportion of cases; it is also well known that some areas located behind the folds are hardly explored in detail by the OC. From the literature, an OC deemed appropriate by a certified operator has a rate of non-recognition of adenocarcinomas and advanced adenomas of 5% and 12%, respectively. Thus, CTC specificity should be considered indicative and not absolute when

TABLE II - Diagnostic performances of 3 readers with a different specific expertise, considering per-patient data: reader 1 had more than 1000 CTC, reader 2 about 200 CTC and reader 3 was in its learning curve.

	Reader 1	Reader 2	Reader 3
True positive	17	16	12
True negative	30	29	29
False positive	2	3	3
False negative	4	5	9
Sensitivity	80,95%	79,16%	57,14%
Specificity	93,75%	85,29%	90,62%
PPV	89,47%	84,21%	80%
NPV	88,24%	85,29%	76,32%
Accuracy	88,68%	84,91%	77,36%

TABLE III - Diagnostic performances of the 3 human readers, related to the final pathological characterization of the lesions.

Final pathology	N.	Reader 1	Reader 2	Reader 3
Infiltrating adenocarcinoma	4	4	4	4
In situ adenocarcinoma	4	3	3	3
Low-grade adenoma	43	21	18	12
Non adenomatous lesion	24	5	2	2

calculated in respect to OC. It would have been interesting to repeat OC, with specific targeting of flat lesions recognized by CTC and not by OC, with the aim to verify if in some cases CTC sensitivity has proven to be even higher than OC.

In the present work we decided to include flat lesions with a height of less than 3 mm, including those with more than 10 mm diameter. At the same time, we decided to exclude all the OC in which the bowel cleansing and the quality of the examination had not been judged excellent by the operator. With these specifications, the sensitivity of CTC for flat lesions was extremely low, ranging from 44% of the skilled reader to less than 30% of the reader in the learning curve. In fact, numerous lesions were not recognized. This was lower than the 82-92% sensitivity achieved for adenomatous polypoid lesions in several major trials^{4,5}. Nevertheless, the sensitivity for nonpolypoid lesions in the present series is better than previously reported by Park et al.⁸ (25% for nonpolypoid adenomatous lesions 9 mm or larger), but another paper from the same group⁷ recently reported an improved sensitivity at 66.7% for adenomatous lesions and 90% for adenocarcinomas; the Authors believed actual relatively high sensitivity to be related to parameters of high-quality CTC such as good bowel preparation and colon distention, the use of primary 3D interpretation and readers familiarity with nonpolypoid colorectal lesions. Indeed, in the first series the Authors

did not use fecal tagging and probably this was the decisive improvement. Many Authors actually underline that a proper CTC technique could achieve high diagnostic accuracy^{5,21,22,23}. In another series, Pickhardt et al.¹⁶ reported a very good sensitivity for nonpolypoid adenomas (82.8%, or 24/29) with > 6 mm size, defining nonpolypoid lesion as ≤ 3 mm in height, but also including higher lesions in the series. The overall sensitivity obtained is in line with that (47.6%) published recently by Sakamoto et al. on a series of 42 flat lesions²⁴. The sensitivity of the present series is partially affected by the fact that 2 out of 21 patients with flat lesions had numerous lesions (respectively 18 and 21), the vast majority of which were not recognized by CTC. However, it must also be said that in one of these two cases the endoscopist has been aided in the identification of lesions from a spread state of melanosis coli that by virtue of the gradient color of the mucosa has facilitated the diagnosis.

In fact, per-patient are clearly better than per-lesion data analysis, with sensitivity of 80% and NPV close to 90% for the expert reader (reader 1). Is the per-lesion or the per-patient diagnostic performance more important? This is clearly related to the setting of CTC; for screening purpose, the NPV is of upmost importance, so per-patient performances should mainly be considered.

On the other hand, it is essential to understand how the lack of recognition of a nonpolypoid lesion may influence the patient prognosis. In our work, all the lesions corresponding to infiltrating adenocarcinomas were found, as well as 3 out of 4 of stage Tis adenocarcinomas, while 22/43 lesions corresponding to low-grade dysplastic adenomas and 19/24 non adenomatous lesions have not been recognized also by reader 1. Which means that after a negative CTC, the patient can expect to have a probability near to 50 % to have an eventual flat lesion with low-grade dysplasia undiagnosed; in any case for these lesions, notoriously with a low evolutionary potential, a follow-up with CTC after 2-3 years would be enough. In particular, it seems of considerable value the fact that the sensitivity for not adenomatous lesions is very low, which could prove an advantage rather than a limit, as pointed out by Park and by others^{7,15,16,25}. One plausible explanation for this finding may be the tendency of nonadenomatous lesions to efface with air distention²⁶.

Obviously these considerations should be correlated with the actual prevalence of flat lesions in the population, which is not still clearly defined, for the shortage of epidemiological data and the variability of the definitions. In particular, Soetikno et al., applying the old definition of nonpolypoid lesions (height less than half the greatest lesion diameter), reported that 5.84% (36/616) and 0.32% (2/616) of patients had nonpolypoid lesions and nonpolypoid stage Tis-T1 adenocarcinomas in their screening database, respectively¹³. O'Brien et al. reported that about a third of adenomas detected on

colonoscopy in the National Polyp Study²⁷ were non-polypoid, according to the definition of histologically estimated adenoma thickness 1.3 mm or less (in this study, also cases with a maximum diameter lower than 5 mm were included).

A significant difference was found between three human radiologist readers with a different degree of experience (Fig. 1); in fact, this represent in our view the main factor influencing diagnostic performance of CTC. In the literature there are few studies upon the interobserver agreement in CTC examinations and those found are outdated, dating back to "pre-faecal tagging times" and don't consider the novice reader. The novice reader, named in this study as reader 3, is the one that is considered in the course of learning, the one who has less than 164 examinations performed²⁸ and in particular less than 50 cases according to what has been reported by Burling et al.²⁹ and by the ESGAR CTC Group investigators³⁰. Moreover, no study considers the agreement for detection of flat lesions by radiologists with different experience in virtual colonoscopy.

Limitations of this study are the absence of information about the maximum size of the lesion (this was because there is no clear agreement in the management of colorectal lesions directly relating to the maximum size, and this paper was specifically focused on the diagnostic performance with flat lesions, independently from the maximum size) and the absence of Paris II-b lesions.

Riassunto

Scopo dello studio è determinare l'accuratezza diagnostica della Colon TC per l'individuazione di lesioni coloretali non polipoidi.

Durante il periodo 2010-2011, 51 di 454 pazienti candidati a Colon TC sono stati successivamente sottoposti a colonoscopia. I parametri utilizzati per la classificazione delle lesioni sono stati: spessore massimo di 3 mm per lesioni piatte, diametro massimo di 10 mm di Laterally spreading Tumors (LST). Le immagini sono state interpretate da 3 distinte équipes con differente esperienza. Un totale di 75 lesioni coloretali non polipoidi sono state identificate in 21 pazienti, 43 di tipo II-A con adenoma a displasia a basso grado, 2 di tipo II-C adenocarcinomi intramucosi, 2 LST con adenocarcinoma intramucoso, 24 lesioni non adenomatose iperplastiche, 4 LST con adenocarcinoma infiltrante (T1N0M0 in 2 casi T2N0M0). La sensibilità e la NPV calcolate per singola lesione sono risultate 44% e 80.5%, mentre la sensibilità, PPV, NPV e l'accuratezza per singolo paziente sono risultate 80.9%, 93.7%, 89.5%, 88.2%, 88.7%. L'interpretazione delle immagini è risultata significativamente determinata dall'esperienza degli esaminatori ($p=0.072$ and $p=0.030$). Tutti i carcinomi infiltranti ed il 75 % dei TIS sono stati identificati da entrambe le metodiche diagnostiche.

Conclusione: La Colon TC ha mostrato un'alta accuratezza nell'identificazione di neoformazioni per ogni singolo paziente, considerando lesioni coloretali non polipoidi oltre ad un'alta capacità di identificare carcinomi non polipoidi. L'identificazione delle lesioni è strettamente correlata all'esperienza nella lettura di tali immagini.

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