REVIEW
235 Detecting circulating tumor material and digital pathology imaging during pancreatic cancer progression
Moravec R, Divi R, Verma M

ORIGINAL ARTICLE
Retrospective Cohort Study
251 Value of macrobiopsies and transanal endoscopic microsurgery in the histological work-up of rectal neoplasms: A retrospective study
Bökkerink GMJ, van der Wilt GJ, de Jong D, van Krieken HHJM, Bleichrodt RP, de Wilt JHW, Bremers AJA

Retrospective Study
257 Effects of age on survival and morbidity in gastric cancer patients undergoing gastrectomy

CASE REPORT
263 Gastric plexiform fibromyxoma resected by endoscopic submucosal dissection after observation of chronological changes: A case report
ABOUT COVER

Editorial Board Member of World Journal of Gastrointestinal Oncology, Stefan Boeck, MD, Associate Professor, Department of Internal Medicine III, Ludwig-Maximilians-University of Munich, D-81377 Munich, Germany

AIM AND SCOPE

World Journal of Gastrointestinal Oncology (World J Gastrointest Oncol, WJGO, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of WJGO include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to WJGO. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Gastrointestinal Oncology is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central.

FLYLEAF

I-IV Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: Xiang Li
Responsible Electronic Editor: Ye-Jing Lu
Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hsin-Chen Lee, PhD, Professor, Institute of Pharmacology, School of Medicine, National Yang-Ming University, Taipei 112, Taiwan
Dimitrios H Roukoun, MD, PhD, Professor, Personalized Cancer Genomic Medicine, Human Cancer Biobank Center, Ioannina University, Metabatiko Ktirio Panepistimiou Ioanninon, Office 229, Ioannina, TK 45110, Greece

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/1948-5204/editorialboard.htm

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Gastrointestinal Oncology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
June 15, 2017

COPYRIGHT
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution-Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non-commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/getinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com
Value of macrobiopsies and transanal endoscopic microsurgery in the histological work-up of rectal neoplasms: A retrospective study

Guus MJ Bökkerink, Gert-Jan van der Wilt, Dirk de Jong, Han HJM van Krieken, Robert P Bleichrodt, Johannes HW de Wilt, Andreas JA Bremers

AIM
To evaluate a step up approach: Taking macrobiopsies and performing excision biopsies in patients with suspected rectal cancer in which biopsies taken through the flexible endoscope showed benign histology.

METHODS
Patients with a rectal neoplasm who underwent flexible endoscopy and biopsies were included. In case of benign biopsies rigid rectoscopy and macrobiopsies were performed. The definitive surgery was supervised by Bleichrodt RPB and Bremers AJA.

Abstract

AIM
To evaluate a step up approach: Taking macrobiopsies and performing excision biopsies in patients with suspected rectal cancer in which biopsies taken through the flexible endoscope showed benign histology.

METHODS
Patients with a rectal neoplasm who underwent flexible endoscopy and biopsies were included. In case of benign biopsies rigid rectoscopy and macrobiopsies were performed.
employed. If this failed to prove malignancy, transanal endoscopic microsurgery (TEM) was used in a final effort to establish a certain preoperative diagnosis. The preoperative results were compared with the findings after surgical excision and follow up to calculate the reliability of this algorithm.

RESULTS
One hundred and thirty-two patients were included. One hundred and ten patients with a carcinoma and 22 with an adenoma. Seventy-five of 110 carcinomas were proven malignant after flexible endoscopy. With the addition of rigid endoscopy and taking of macrobiopsies, this number increased to 89. Performing TEM excision biopsies further enlarged the number of proven malignancies to 100.

CONCLUSION
The step-up approach includes taking macrobiopsies through the rigid rectoscope and performing excision biopsies using transanal endoscopic microsurgery in addition to flexible endoscopy. This approach, reduced the number of missed preoperative malignant diagnoses from 32% to 9%.

Key words: Rectal cancer; Histology; Biopsy; Macrobiopsy; Transanal endoscopic microsurgery; Sampling error

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Increasing the number of biopsies taken through a flexible endoscope, taking macrobiopsies and performing excision biopsies with transanal endoscopic microsurgery can reduce the number of missed preoperative malignant diagnoses in patients with rectal cancer.


INTRODUCTION
Adequate pre-treatment histological sampling is of paramount importance for the optimal treatment of rectal neoplasms. A wide spectrum of surgical and neoadjuvant treatments is available. In case of benign disease, surgical excision alone, will suffice. For a majority of the malignant tumors however, a combination of neoadjuvant therapy and total mesorectal excision is indicated to optimize local control[1-5]. High complete response rates after chemoradiation therapy have led to the development of organpreserving strategies[6-8].

Although the oncological benefits of neoadjuvant treatments are evident, the acute toxicity and long term side effects of chemoradiation therapy are considerable.

Therefore, administration of neoadjuvant chemoradiation therapy requires definite proof of malignancy. As the diagnosis of malignancy based on imaging alone may be erroneous because of the risk of overstaging MRI based imaging, these neoadjuvant treatments require histological evidence of malignancy before treatment can commence.

A preoperative histological diagnosis is usually obtained by taking biopsies through a flexible endoscope. Flexible endoscopy offers a high tumor detection rate and the possibility to take biopsies. However, from limited evidence available, sensitivity for malignancy on these biopsies is suboptimal at best[10-12]. The most important reason for this is that biopsies taken through flexible endoscopes are small and sometimes too superficial to demonstrate high grade neoplasia[13]. In case of superficial biopsies, the diagnosis of malignancy relies solely on tissue structure and atypical appearance of cells (Figure 1). One way to overcome this problem is to take more biopsies. Indeed, several authors demonstrated a correlation between sensitivity and the number of biopsies taken from a suspected lesion. When 3 or 4 biopsies were taken, the sensitivity for invasive growth varied between 50% and 86%[10-12]. By taking up to 10 biopsies, the sensitivity increased to 78% to 100% (Table 1).

Another way to increase the sensitivity of pre-treatment histological sampling for the detection of malignancy is to increase the volume and depth of the biopsy. Although considered old-fashioned by many clinicians, rigid rectoscopy is an easy, cost effective, fast and well-tolerated tool for examination of the rectum[14], that enables the endoscopist to take so-called “macrobiopsies”. Macrobiopsies are 2-10 times larger in three dimensions and approximately 50 times larger in volume than those obtained with flexible rectoscopy. The
rigidity of the biopsy forceps also enables the endoscopist
to push the forceps against the tumor so that deeper
layers of the rectal wall can be included in the biopsy, and
to “palpate” the lesion and take the biopsies from the
firmer parts of the lesion selectively. For these reasons,
rigid rectoscopy may perform better with respect to
sampling error than flexible endoscopy.

Sometimes, even macrobiopsies may fail to demon-
strate invasive growth. In an ultimate effort to obtain
sufficient histological confirmation of malignancy without
interfering with the optimal treatment strategy, transanal
endoscopic microsurgery (TEM) may be used in these
cases to perform an excision biopsy. TEM is an invasive
way to obtain a histological diagnosis. However, it does
have the advantage that it can sometimes be used as a
definitive treatment for low risk T1 carcinomas.

Although there are sound theoretical grounds to
expect that rigid rectoscopy and TEM can boost the
sensitivity of the pre-treatment histological work-up for
suspected rectal cancer, this has never been empirically
investigated. The aim of this article, therefore, is to
assess the accuracy, therapeutic value and tolerability of
taking additional macrobiopsies and performing excision
biopsies with TEM in patients with suspected rectal
cancer: a step-up approach.

**MATERIALS AND METHODS**

**Patients**
All patients who underwent biopsy through a flexible
endoscope, as part of the work-up for surgery of a rectal
neoplasm, between January 2005 and January 2011
in the Radboud University Nijmegen Medical Center,
Nijmegen, The Netherlands were analyzed. Patient
selection was based on the database of surgical procedure
in our hospital. All patients who underwent surgical
excision of a rectal neoplasm (local excision; transanal
endoscopic microsurgery or total or partial mesorectal
excision: Abdominoperineal resection or (low) anterior
resection] where selected. The medical records of all
patients were reviewed for demographic characteristics
and for endoscopy, pathology and surgical reports.

**Diagnostic and therapeutic algorithm**
This is a retrospective analysis of the diagnostic and
therapeutic step-up algorithm, which was followed during
the study period. This algorithm is shown in Figure 2.
Macrobiopsies were taken through the rigid sigmoidoscope in case of benign histology after flexible endoscopy and persisting clinical or radiological suspicion for malignancy, macrobiopsies were taken through rigid rectoscopy. TEM was performed in case of a benign or cT1 tumor on endorectal ultrasound (ERUS).

**Equipment**
Flexible endoscopes were the CF140S 70 cm sigmoidoscope and CF 140 l colonoscope (Olympus, Tokyo, Japan). For flexible endoscopy, a 2.2 mm radial jaw biopsy forceps was used (Boston Scientific, Natick, United States) (Figure 1). For colonoscopy complete bowel preparation was used. Sedation and analgesia given upon request. During colonoscopy multiple biopsies were taken from any suspicious lesions. A 250 mm × 18 mm disposable rectoscopy tube, Heine, Herrsching, Germany was used for rigid rectoscopy. Biopsies were taken with a Franital biopsy forceps with a 5 mm × 10 mm bite (Figure 1). Bowel preparation before rigid and flexible sigmoidoscopy consisted of a single soap enema. All procedures were performed by, or under direct supervision of, consultant level surgeons or gastroenterologists.

TEM-surgery was performed by one of the authors (AB) as first described by Buess using the stereo-optic Wolf rectoscope (Wolf; Knittlingen, Germany).

**Statistical analysis**
The additional yield of taking macrobiopsies and per-
forming excision biopsies was analyzed by comparing
all biopsies with the definitive excision specimen. The
differences in sensitivity between the number of samples
taken through the flexible endoscope was tested with the
χ² test for trends.

**RESULTS**

**Patients**
One hundred and thirty-two patients (82 males and 50
females) underwent flexible endoscopy with biopsies as
part of the work-up for a rectal neoplasm (tumor located
below 15 cm from the anal verge). Median age was 63
years (range: 27-92).
Flexible endoscopy

The histological work-up of all 132 patients is shown in Figure 3. At final pathology 110 patients had an adenocarcinoma, of which 75 (68%) were detected with flexible endoscopy only. The other 22 patients had a villous adenoma. One of the tumors, classified as malignant based on biopsies taken through the flexible endoscope (snare polypectomy), showed benign histology after (transanal) resection.

The number of biopsies was documented for 113 patients and varies from 1 to 14, with a median of 4 biopsies (Table 1). There was a significant correlation between the number of biopsies and a correct histological diagnosis \( (P = 0.020; \chi^2 \text{ test for trends}) \). Taking 4 or more biopsies resulted in a significant higher sensitivity than taking 3 or less \( (P = 0.004; \chi^2 \text{ test for trends}) \). Prior probability of malignancy was 83.3% in this group. Sensitivity and specificity were 68% and 95% respectively. A malignant result is useful with a posterior probability of malignancy of 99% (95%CI: 92%-100%). Benign histology after flexible endoscopy is clearly inconclusive, leaving a posterior probability of malignancy of 62% (95%CI: 55%-69%).

Rigid rectoscopy and macrobiopsies

In 29 of the 56 patients who were diagnosed with a benign tumor after flexible endoscopy, additional rigid endoscopy was performed. With this addition, 14 previously undetected carcinomas were diagnosed. In this selected group of 29 patients who underwent rigid endoscopy, prior probability of malignancy was 75.9%. Sensitivity and specificity were 64% and 100% respectively, which makes a malignant histology after rigid endoscopy useful with a posterior probability of malignancy of 100% (95%CI: 68%-100%). Benign histology after rigid endoscopy is leaves a posterior probability of malignancy of 53%

TEM

A total of 44 patients underwent TEM (Figure 3), 32 patients after benign biopsies (combined flexible and rigid), 12 after malignant biopsies (clinical and radiological T1). With this addition, another 11 invasive carcinomas were detected. The number of detected carcinomas increased from 89 out of 110 (81%) to 100 out of 110 (91%).

Histology after TEM showed 18 adenomas, 4 in situ carcinomas, and 22 carcinomas. After TEM, 10 patients underwent a completion TME because of unfavorable histological findings. The excision specimen of one of these 10 patients was perforated at the former local excision site. One patient with an ypT3 tumor was unfit to undergo a total mesorectal excision and was treated with short course radiotherapy and TEM after a 6 wk interval. No major complications were observed nor preoperative perforations or conversions to laparotomy after TEM in this group. One patient with postoperative rectal blood loss needed transfusion.

Neoadjuvant treatment

A total of 79 patients received neoadjuvant treatment in 4 different schemes according to tumor stage and general condition. Thirty-eight patients received 5 Gy \( \times 5 \) Gy in the week prior to surgery according to protocol for T2 and T3 tumors. Thirty Patients with a radiologically involved circumferential resection margin received neoadjuvant chemoradiation therapy (25 Gy \( \times 2 \) Gy with concomitant capecitabine) and delayed surgery after 8 wk. Eleven patients whose general condition did not allow chemoradiation therapy (CRT) and who required tumor regression received 5 Gy \( \times 5 \) Gy \( (n = 9) \) or long course radiotherapy (24 Gy \( \times 2 \) Gy) \( (n = 2) \) and delayed surgery as decided by a multidisciplinary team.

Figure 3 Yield of macrobiopsies en excision biopsies. aFourteen not earlier detected carcinomas; bEleven not earlier detected carcinomas.
Surgery
Forty-four patients underwent TEM, 53 underwent a LAR and a further 34 underwent APR. 1 patient with MSH6 mutation underwent a subtotal colectomy with LAR. After TEM 10 patients underwent a completion TME. Definitive histology after resection showed 18 adenomas, 4 in situ carcinomas, 101 carcinomas and 9 complete responses after neoadjuvant treatment.

DISCUSSION
In the present study we demonstrated that macrobiopsies obtained through a rigid endoscope and excision biopsies by TEM are valuable additional tools to obtain a correct preoperative histological diagnosis in a significant number of patients with suspected rectal cancer.

Over time, flexible endoscopy has replaced rigid rectoscopy because of its superior (videoscopic) visualization of the entire colon, better mobility and deeper intubation[9-20] and subsequently a good tumor detection rate[9]. However, when it comes to the diagnostic sensitivity to detect malignancy in rectal tumors, our results are in accordance with the literature and confirm the disappointing overall performance of flexible endoscopy. The proportion of false negative biopsies after flexible endoscopy alone was 32%. This can be explained by the number of biopsies taken in our study. With a median number of biopsies of 4, a sensitivity of 70% can be expected.

Increasing the number of biopsies with flexible endoscopy can increase the number of detected malignancies in the group of suspicious rectal neoplasms (Table 1). However, increasing the number of biopsies through flexible endoscopy, as suggested by some authors[10-12], was not our main strategy to increase diagnostic sensitivity, because these biopsies are often too superficial to show high grade neoplasia[9]. Our algorithm included rigid endoscopy and TEM as additional steps.

In terms of accuracy, the selected group of patients with false negative biopsies after flexible endoscopy, 14 additional patients with a malignancy were identified with rigid endoscopy, and with TEM, another 11 patients. In total, 100 of 110 malignancies could be diagnosed preoperatively. This means that the proportion of carcinomas of which the malignant nature would have been proven in time was 32% with flexible endoscopy alone and was reduced to 9% in the evaluated algorithm. This is a significant reduction with high therapeutic value.

Regarding procedure-related morbidity, both rigid endoscopy and TEM were well-tolerated. In our experience, TEM did not cause an increase in positive circumferential resection margins (CRM) in TME as determined by standardized pathological evaluation according to Quircke[21].

Conclusion
With the current treatment options for patients with rectal cancer, optimal preoperative histological diagnosis is essential. Besides the combinations with radical surgery, multimodality organ sparing treatments are becoming more and more accepted. Short-term results show high percentages of pathologic complete response[6,22] and acceptable oncological outcome[6,7], adequate histological sampling seems of paramount importance for these new treatment strategies, not only before but also after (chemo)radiation therapy.

In the present study we demonstrated that macrobiopsies obtained through a rigid endoscope and excision biopsies by TEM are valuable additional tools in obtaining a correct preoperative histological diagnosis in a significant number of patients with suspected rectal cancer. Prospective trials are needed to compare the yield of these strategies to increasing the amount of biopsies through flexible endoscopy. Evidence-based recommendations for guidelines regarding the histological work-up of rectal neoplasms can be based on those trials.

REFERENCES


11 Collepriest BJ, Marden PF, Linehan JD. What is the optimal number of biopsies to diagnose a tumor found during colonoscopy? *J Clin Gastroenterol* 2009; 43: 1012-1013 [PMID: 19525860 DOI: 10.1097/MCG.0b013e3181915d0a]


