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Clinical Investigation

Pretreatment Evaluation of Microcirculation by Dynamic Contrast-Enhanced Magnetic Resonance Imaging Predicts Survival in Primary Rectal Cancer Patients

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Summary

Measurement of mean perfusion index before neoadjuvant chemoradiation has potential as an imaging biomarker and could facilitate the long-required therapeutic stratification to distinguish responders from nonresponders. Our results could again demonstrate that pretherapeutic prediction of response to neoadjuvant chemoradiation is feasible. Furthermore, for the first time we are able to predict pretherapeutically disease-free survival and overall survival. Mean perfusion

Purpose: To investigate the prognostic value of the perfusion index (PI), a microcirculatory parameter estimated from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), which integrates information on both flow and permeability, to predict overall survival and disease-free survival in patients with primary rectal cancer.

Methods and Materials: A total of 83 patients with stage cT3 rectal cancer requiring neoadjuvant chemoradiation were investigated with DCE-MRI before start of therapy. Contrast-enhanced dynamic T_1 mapping was obtained, and a simple data analysis strategy based on the calculation of the maximum slope of the tissue concentration−time curve divided by the maximum of the arterial input function was used as a measure of tumor microcirculation (PI), which integrates information on both flow and permeability.

Results: In 39 patients (47.0%), T downstaging (ypT0-2) was observed. During a mean (±SD) follow-up period of 71 ± 29 months, 58 patients (69.9%) survived, and disease-free survival was achieved in 45 patients (54.2%). The mean PI (PImean) averaged over the group of nonresponders was significantly higher than for responders. Additionally, higher PImean in age- and gender-adjusted analyses was strongly predictive of therapy nonresponse. Most importantly, PImean strongly and significantly predicted disease-free survival (unadjusted hazard ratio [HR],

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index may represent a new valuable and practical tool of therapeutic stratification.

1.85 [95% confidence interval, 1.35-2.54; $P<.001$)]; HR adjusted for age and sex, 1.81 [1.30-2.51]; $P<.001$) as well as overall survival (unadjusted HR 1.42 [1.02-1.99], $P=.040$; HR adjusted for age and sex, 1.43 [1.03-1.98]; $P=.034$).

Conclusions: This analysis identifies PImean as a novel biomarker that is predictive for therapy response, disease-free survival, and overall survival in patients with primary locally advanced rectal cancer.

Introduction

Neoadjuvant chemoradiation followed by total mesorectal excision is the standard treatment for locally advanced rectal cancer (clinical TNM stage II-III), even though the responsiveness varies from complete response to resistance (1). The ability to downstage tumors, increase the potential for sphincter-saving surgery, reduce local recurrence, and improve survival has made neoadjuvant chemoradiation an attractive therapeutic option (2-4). Any response to neoadjuvant chemoradiation seems to improve outcomes. However, only a subgroup of patients shows response, whereas for other patients the consequences of chemotherapy- and radiation therapy—related toxicity outweigh the benefits (5-7). For some patients high-quality surgery suffices, and for others a combination of radiation therapy, chemotherapy, and surgery is needed. Therefore improvements are needed to predict local outcome as well as disease-free survival (DFS) and overall survival (OS) of neoadjuvant chemoradiation. Currently available prognostic factors (8, 9), such as clinical staging and histology, do not always predict therapy outcome effectively.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a noninvasive functional imaging technique for measuring properties of tumor microcirculation and is used in a variety of clinical situations. Dynamic contrast-enhanced magnetic resonance imaging has been investigated for cancer detection, diagnosis, staging, and assessment of treatment response (10-15).

Our study group recently calculated the so-called perfusion index (PI), a microcirulatory parameter estimated from DCE-MRI that combines information about permeability and blood volume and takes the arterial input function into account.

The aim of this study was to investigate the prognostic relevance of the mean PI (PImean) after a sufficient follow-up, for therapy response, DFS, and OS in cT3 rectal cancer patients.

Methods and Materials

Eligibility and enrollment

In this prospective imaging study patients were eligible for DCE-MRI examination if they had histologically confirmed diagnosis of locally advanced adenocarcinoma of the rectum without distant metastases (cT3NxM0 according to the 1997 International Union Against Cancer staging system) and were scheduled for neoadjuvant chemoradiation therapy. The extent of disease was assessed by clinical examination, colonoscopy, and computed tomography of the chest, abdomen, and pelvis. Endoscopic ultrasonography and diagnostic MRI were performed in each patient for determining the locoregional stage of the rectal tumor.

We excluded patients with tumor invasion of the sphincter, previous surgical intervention or radiation in the area of the abdomen, previous chemotherapy, patients with second malignancies, or contraindications for the DCE-MRI examination.

For each tumor, therapy outcome was classified either as "therapy response," if the pathologic observation revealed no invasion into the perirectal fat (ypT0-2), or as "therapy nonresponse," if the observation yielded invasion (ypT3).

The trial was approved by the local institutional review board and was carried out in accordance with the Helsinki declaration of 1975, as revised in 1983. Written informed consent was obtained from all patients before study inclusion.

Treatment technique

Each patient received neoadjuvant combined chemoradiation. Three-dimensional conformal radiation therapy was planned using a linear accelerator with photon energies of 4 MV or more. Clinical target volumes (CTVs) included the primary rectal tumor lesions and the 2 end portions of the rectum; the perirectal tissues; and the anterior sacral lymph, iliac lymph, obturator lymph, and true pelvis internal iliac lymph drainage areas. For patients with stage T4 lesions or tumors invading the bladder, the CTV also included the external iliac lymph drainage area. Planned target volume is defined as CTV or gross tumor volume plus 8 mm. The treatment was given in the prone position with a full bladder. Customized beam blocks or multileaf collimators were used to restrict the irradiation volume to the treated volume. A dose of 45 Gy was planned over 5 weeks, 1.8 Gy per fraction, all fields being treated daily. The reference dose was specified at the intersection of the beam axis. The target absorbed dose was at least 95%, and the maximum was not higher than 107% of the reference dose (16). Radiation was discontinued if grade 4 toxicity according to the National Cancer Institute Common Terminology Criteria guidelines occurred. Preoperative chemotherapy was administered on each treatment day. Fluorouracil (5-Fluorouracil "Ebeve";