European Journal of Cancer (2014) **50**, 2958–2965

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Frequency of therapy-relevant staging shifts in colorectal cancer through the introduction of pN1c in the 7th TNM edition

M. von Winterfeld [a,1], M. Hoffmeister [b,1], B. Ingold-Heppner [a], L. Jansen [b], S. Tao [b], E. Herpel [c,d], P. Schirmacher [c], M. Dietel [a], J. Chang-Claude [e], F. Autschbach [f], H. Brenner [b], H. Bläker [a,c,*]

[a] *Institute of Pathology, Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany*
[b] *Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany*
[c] *Institute of Pathology, University of Heidelberg, Im Neuenheimer Feld 220/221, 69120 Heidelberg, Germany*
[d] *Tissue Bank of the National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 460, 69120 Heidelberg, Germany*
[e] *Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer 581, 69120 Heidelberg, Germany*
[f] *Institute of Pathology, SLK-Clinics Heilbronn, Am Gesundbrunnen 20-26, 74078 Heilbronn, Germany*

Received 6 June 2014; received in revised form 1 September 2014; accepted 10 September 2014
Available online 30 September 2014

KEYWORDS
Colorectal cancer
Tumour deposits
pN1c

Abstract ***Background:*** pN1c is a novel N-category introduced for colorectal cancer (CRC) in current TNM (Tumour, Node, Metastasis) classification. It represents cancers displaying tumour deposits (TDs) in the fat but no involvement of lymph nodes. pN1c is integrated into the UICC (International Union Against Cancer) staging system and shifts previous stage II cancers (6th edition) to stage III. We investigated the frequency of upstaging and TD prognostic significance.

Methods: 414 CRCs, consecutively collected during a population-based epidemiological study, TNM classified and UICC staged according to the 6th TNM edition were reinvestigated for TD presence. The association with survival was investigated after a median follow-up time of 5 years in multivariate analyses among nodal negative and positive cases.

Results: TDs were found in 103 (24.9%) cancers and were strongly associated with T-, N- and M-stages ($p < 0.0001$, each). Upstaging of previous stage II cancers by the presence of TDs (pN1c) was found in six of 140 cases (4.3% of stage II, 1.4% of all tumours). For stage III CRC, strongly reduced overall, CRC-specific and recurrence-free survival were observed with

* *Corresponding author at:* Institute of Pathology, Charité University Medicine Berlin, Charitéplatz 1, 10117 Berlin, Germany. Tel.: +49 30 450 536 276.
E-mail address: hendrik.blaeker@charite.de (H. Bläker).
[1] M.v.W. and M.H. contributed equally to this study.

http://dx.doi.org/10.1016/j.ejca.2014.09.002

the presence of TDs (hazard ratios (HR) 2.29, 95% confidence interval 1.27–4.10, HR 2.51, 1.27–4.98, and HR 2.43, 1.32–4.48, respectively).

Conclusions: Upstaging of CRCs through the introduction of pN1c occurs in less than 5% of previous stage II and less than 2% of all cancers. Given the biologic relevance of TDs, integration into the UICC staging relevant N-category is justified. The high prognostic impact of TDs, however, is not reflected in nodal positive cancers in both the TNM and UICC staging systems.

1. Introduction

Tumour deposits (TDs), also known as tumour nodules [1] or extrabowel skipped cancer infiltrations [2], are common features in colorectal cancer (CRC), described in 15–30% of cases [2–5]. They are defined as focal aggregates of carcinoma tissues in the pericolic or perirectal fat lacking contact to the primary tumour and to the lymph nodes. Their first descriptions date back to the mid thirties of the last century [6,7], when they were considered soft tissue metastases resulting from vascular tumour infiltration. In fact, most TDs present a local metastatic spread via blood and/or lymphatic vessels, only a minority of these lesions originate from nerve sheath infiltrations or demonstrate continuity with the primary tumour in serial sections [8,9].

TDs were considered in the TNM classification since 1997. In the 5th edition [10,11] it was recommended to classify TDs of at least 3 mm (size rule) as lymph node metastasis and to integrate TDs less than 3 mm into the T-category. In the 6th edition [12,13] this size rule was replaced by a contour rule. TDs with a smooth contour were counted as lymph node metastasis whilst those with irregular shape were integrated into the T-category and scored as venous vessel invasion (pV1). The present 7th edition of the TNM classification [14,15] recommends to count TDs with a smooth contour as lymph node metastasis and to classify TDs with irregular shape as pN1c, and no longer as pV1. Other than pV1, pN1c is staging relevant. According to the current TNM edition the presence of TDs always results in a UICC stage of at least III and consequently adjuvant chemotherapy is routinely administered.

Several studies have shown an adverse outcome for CRCs with TDs and the prognostic impact of TDs in lymph node negative cancers has been investigated [1,3,4,16]. These studies, however, were performed on selected UICC stages or investigated the prognostic significance of all TDs, not only those considered for the pN1c category.

In order to evaluate the general relevance of the potential upstaging due to the introduction of pN1c and to investigate the significance of TDs for prognosis we reanalysed 414 consecutively recruited yet otherwise unselected cases of CRC, that were TNM classified and staged according to the 6th edition, for the presence of TDs and compared these data to the cancer specific follow up.

2. Patients and methods

2.1. Study population

Patients were participants of the DACHS study (DACHS: Darmkrebs, Chancen der Verhütung durch Screening) a population based epidemiological case-control study of CRC with follow-up of patients. All patients had a histologically confirmed first diagnosis of primary CRC and were eligible for recruitment if they were at least 30 years old, physically and mentally able to participate in an interview, sufficiently proficient in German language and resident in the study region. More details about patient recruitment and tissue processing in the DACHS study have been previously reported [17,18]. Of 1975 CRCs diagnosed in 2003–2007 and enrolled in DACHS, 427 had been histologically investigated and TNM classified at the Institute of Pathology, University of Heidelberg, and were included in this study.

2.2. Data collection and follow-up

The patients provided information during a face-to-face interview which was conducted by trained interviewers. In addition, discharge letters and pathology reports were collected. On average 3 years after diagnosis, a questionnaire was sent to the treating physicians of the patients to collect information on CRC therapy, and intermittent diagnoses of concomitant diseases and potential CRC recurrence.

Five years after diagnosis, additional information was collected from the patients alive, again including questions on newly diagnosed diseases and recurrences. New diagnoses and cancer recurrences were verified through medical records of the attending physicians. For those alive at 3-year but not at 5-year follow-up information about recurrence of disease for this period was requested directly from the physicians. Data on vital status and date of death were obtained from the population registries. Causes of death were verified by death certificates obtained from the health authorities in the Rhein-Neckar-Odenwald region and coded