Pathology – Research and Practice 212 (2016) 73–76

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Original article

The Petersen prognostic index revisited in Dukes B colon cancer – Inter-institutional differences

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ARTICLE INFO

Article history:
Received 14 March 2015
Received in revised form 12 June 2015
Accepted 14 August 2015

Keywords:
Colon cancer
Prognostic index
Stage II
Dukes' B

ABSTRACT

A prognostic index (Petersen index, PI) was created for patients with pT3-4 pN0 M0 (Stage II, Dukes' B) colon cancers to distinguish between patients with better and worse outcome, and to help in recommending adjuvant chemotherapy for high risk patients in this stage.

The prognostic value of the PI was evaluated in two independent retrospective series of stage II (Dukes' B) colon cancer patients. The parameters defining the PI (venous invasion, peritoneal involvement, circumferential margin involvement, perforation through the tumour) and performance of the PI were compared in two institutions.

The two series of patients consisted of 127 and 87 patients. Venous invasion was more frequently detected at one of the centres ($p < 0.01$) and tumour perforation was more frequent at the other ($p < 0.01$). There were no significant differences in the 5-year survival estimates of all patients ($p = 0.19$), and of either the low PI value groups ($p = 0.52$) or that of the high PI value groups ($p = 0.99$) between the two sites. In contrast, there were significant differences in the survival estimates between patients of the low PI category and those of the high PI category altogether ($p < 0.01$) and in either centre.

Although, it was expected that differences in the frequency of the parameters involved in the PI would influence its performance, this was not confirmed by the data. Our results suggest that using the PI may be of value in prognostic factor based therapy selection of colon carcinoma patients.

Introduction

In 2002, Petersen and colleagues have introduced a prognostic index (further referred to as the Petersen index or PI in this text) based on easily determined morphologic criteria for patients with pT3-4 pN0 M0 (Stage II, Dukes' B) colon cancers [1] to help the selection of patients requiring adjuvant chemotherapy [2]. The index was derived from the follow-up data of 268 patients with colon carcinoma of this stage and included scores based on peritoneal involvement, venous spread, surgical margin involvement and perforation through the tumour. A low PI value (0 or 1) was associated with better 5-year survival than a PI value reflecting high risk (2–5; 86% vs. 50%) [2].

Dukes' B colon cancer patients are often recommended adjuvant chemotherapy on the basis of clinical and pathological parameters like bowel obstruction, less than 12 lymph nodes examined, high grade, lymphatic or venous invasion, perineural invasion, localized perforation and positive, close or undetermined margins [3]. As highlighted above, some of these features are the components of the PI. This retrospective study was aimed at evaluating the prognostic value of the PI in two independent series of colon cancer patients and to compare its composing parameters and performance in two institutions.

Materials and methods

Colon cancer patients operated on for stage II (Dukes' B) disease were selected from the archives of the Department of Pathology of the Bács-Kiskun County Teaching Hospital (BKCH), Kecskemét,

Abbreviations: BKCH, Bács-Kiskun County Teaching Hospital; PI, Petersen index; SU, Semmelweis University.

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http://dx.doi.org/10.1016/j.prp.2015.08.006
0344-0338/

Hungary and the 2nd Department of Pathology, Semmelweis University (SU), Budapest, Hungary. Only patients with available clinical data were included in the study.

The tumours were grossed and assessed according to the relevant general guidelines. However, an elastic stain was routinely used on tumour containing blocks at the BKCH. The pathology records, including the clinical manifestation of the tumours, their gross and microscopic assessments were evaluated for the components of the PI. Follow-up data were available from hospital charts. As patient migration between medical centres is more frequent in Budapest, the follow-up data, especially regarding adjuvant treatments were less accessible for the patients from the SU (Table 1).

The distributions of the categorical variables were compared with the chi-square test or the Fisher exact test, when the numbers were low. Continuous variables were compared with the *t*-test for independent samples. Five-year overall survival estimates were derived with the Kaplan and Meier method. The statistical analyses were performed with VassarStats v.2014 (Richard Lowry, Poughkeepsie, NY, USA) or IBM SPSS 21 Software Package (IBM, Inc., Armonk, NY, USA).

This non-interventional validation study was approved both by the Institutional Review Boards of the BKCH (IKEB #2/140604) and SU (IKEB #207/2011).

Results

There were 127 patients (operated on between January 2007 and December 2010) and 87 patients (operated on between January 2006 and December 2012) included in the analysis from the first (BKCH) and the second centre (SU), respectively. The main characteristics of the two groups are summarized in Table 1. Of the components of the PI, the frequency of venous invasion and tumour perforation was significantly different in the two groups.

The median follow-up period was clearly longer in case of patients from the BKCH (Table 1). Thirty patients of the BKCH group (24%) died during the follow-up period, 11 of their disease and 19 of unrelated causes. Seven patients died in the SU group (8%), five of their disease and two of unknown causes. The number of patients actually having a follow-up period of at least 5 years was 36 (28%) for BKCH and 15 (17%) for SU. The median follow-up periods of surviving patients were 51 months (range 13–80) and 44 months (range 11–94) at the BKCH and SU, respectively after the exclusion of those lost to follow-up.

There were no significant differences in the 5-year Kaplan–Meier survival estimates of all patients ($p = 0.19$, not shown), and of either the low PI value groups ($p = 0.52$) or that of the high PI value groups ($p = 0.99$) between the two sites (Fig. 1). In contrast, there were significant differences in the survival estimates between patients of the low PI category and those of the high PI category altogether ($p = 0.0001$, not shown) and in either centre (Fig. 2). At the BKCH, two of the seven high PI category patients received adjuvant systemic therapy; of the remaining five, three did not survive long enough to receive such a treatment. At the SU, at least nine of the high PI group patients were administered an adjuvant (mostly 5-fluorouracil and platinum-based) chemotherapy regimen.

Discussion

The combination of vascular invasion, peritoneal involvement, positive circumferential margin and perforation through the tumour into the Petersen index resulted in a potent prognosticator [2], and the survival of patients belonging to the low and high PI category demonstrated significant differences in survival in both the individual series studied in the present retrospective work and the series combined. This confirms the prognostic value of the PI. Although there were some differences in the incidence of the variables determining the index and in the proportion of the patients receiving adjuvant systemic treatment between the two sites of the study, there were no significant differences in the 5-year overall survival estimates of the given prognostic categories (low or high PI value) between the two sites.

Of prognosticators of colorectal cancer, peritoneal invasion and extramural venous invasion were classified as category I prognostic factors (with proven prognostic value) by the College of American Pathologists consensus statement, whereas margin involvement was rated as a category IIA (a factor with promising prognostic value tested in clinical trials) [4,5]. Tumour perforation was not listed under categories I and II, and therefore must have been put into category III. However, perforation through the tumour had the highest impact on outcome in the original series describing the PI, and therefore its weigh in contributing to the index is double of that of the three other parameters [2]. Tumour perforation was rare altogether, but was significantly higher at the SU in this comparative study. As patients with this presentation are uncommon, and the present patient cohorts are relatively small, it seems likely that this difference in frequency between the two sites was by chance only.

Circumferential margin involvement is also an obvious factor associated with shorter survival [6], and is often associated with advanced tumour stage [7]. Most (16/19) patients with positive radial margins in a series assessing right hemicolectomy specimens had node-positive colon cancers [7], and these tumours were excluded from the present study. The fact that the frequency of this feature was relatively low in both series is most likely to be related to the less advanced stage of the cancers studied.

Peritoneal involvement by colorectal cancer allows for transperitoneal dissemination of cancer and is therefore an obvious factor of poor prognosis [8]. It is not uncommonly seen in crevices of the peritoneal surface [9], and likewise, specifically looking for these areas has multiplied the incidence of this phenomenon at the BKCH when year 1997 was compared with 2006 (unpublished data). There was no significant difference in the incidence of this parameter between the two series compared.

Several studies have enforced the view that both intramural and extramural venous invasion impact on the outcome of disease, and distinguishing between the two might not be necessary [2,10,11], although there are reports suggesting the extramural venous invasion may reflect worse prognosis [12]. The search for venous invasion on conventional haematoxylin and eosin stained histology slides may not reveal all instances of the phenomenon present on the slides, and elastic stains have been reported to increase the detection rate of such vascular invasion [11,13–17]. Moreover, elastic stain detected venous invasion but not haematoxylin and eosin detected venous invasion was reported to be associated with the development of synchronous or metachronous distant metastases [17]. Better survival rates have been associated with the lack of venous invasion if this was established on the basis of an elastic stain [18–20]. The use of elastic stains has also been reported to improve reproducibility of diagnosing venous invasion in one study [21], but failed to result in the same improvement in another [22]. With caution in interpretation [23], routine elastic stains are a relatively cheap option to gain relevant prognostic information. Routine use of orcein, as an elastic stain for colorectal cancer specimens was introduced at the BKCH in 2007, and therefore involved all cases evaluated in this study. Elastic stains were used per individual preference of the pathologist (in nine cases out of 87, representing 10.3%) at SU. Consequently, the incidence of venous invasion was significantly higher at BKCH. This discrepancy may also highlight the need for a more standardized reporting of vascular invasion. Treatment guidelines advise adjuvant systemic therapy in stage II (Dukes'B) colon cancer with venous invasion [3].