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PET/CT in rectal cancer radiotherapy

Nomogram predicting response after chemoradiotherapy in rectal cancer using sequential PETCT imaging: A multicentric prospective study with external validation

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ABSTRACT

Purpose: To develop and externally validate a predictive model for pathologic complete response (pCR) for locally advanced rectal cancer (LARC) based on clinical features and early sequential ^{18}F-FDG PETCT imaging.

Materials and methods: Prospective data (i.a. THUNDER trial) were used to train (N = 112, MAASTRO Clinic) and validate (N = 78, Università Cattolica del S. Cuore) the model for pCR (ypT0N0). All patients received long-course chemoradiotherapy (CRT) and surgery. Clinical parameters were age, gender, clinical tumour (cT) stage and clinical nodal (cN) stage. PET parameters were SUV_{max}, SUV_{mean}, metabolic tumour volume (MTV) and maximal tumour diameter, for which response indices between pre-treatment and intermediate scan were calculated. Using multivariate logistic regression, three probability groups for pCR were defined.

Results: The pCR rates were 21.4% (training) and 23.1% (validation). The selected predictive features for pCR were cT-stage, cN-stage, response index of SUV_{mean} and maximal tumour diameter during treatment. The models' performances (AUC) were 0.78 (training) and 0.70 (validation). The high probability group for pCR resulted in 100% correct predictions for training and 67% for validation. The model is available on the website www.predictcancer.org.

Conclusions: The developed predictive model for pCR is accurate and externally validated. This model may assist in treatment decisions during CRT to select complete responders for a wait-and-see policy, good responders for extra RT boost and bad responders for additional chemotherapy.

Early prediction of pathologic complete response (pCR) for locally advanced rectal cancer (LARC) patients is valuable because it allows for individualized treatment reorientation [15,28]. The standard treatment for LARC patients is preoperative chemoradiotherapy (CRT) followed by surgery. The neo-adjuvant treatment, intended to control pelvic disease and improve the chance of sphincter preservation, results in a pathological complete response (pCR) in 15–30% of the patients [9,21]. For these complete responders a wait-and-see policy after CRT is a possibility in order to reduce treatment-related morbidity and mortality, for which excellent results are reported [20]. This decision requires however very accurate predictions and assessment of complete response. Other treatment options under consideration are a radiotherapy boost after CRT for good responding patients to achieve more pCRs [8] and additional chemotherapy administration after CRT for the worst responding patients [3]. Both of these options require an early assessment of response even during CRT. Currently, the leading candidate predictive marker for histopathological response prediction in LARC is ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. A meta-analysis from 2012 confirmed the added value of PET imaging, especially for intermediate PET imaging (during CRT) [31]. However, most studies evaluated pre-CRT versus post-CRT PET imaging. Besides that early prediction is preferred for treatment reorientation, later pre-

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dictions may also be affected by CRT-induced inflammatory tissue, which presents tumour equivalent signal on FDG-PET scans [26]. This recognition resulted in more early response assessment studies in the last few years (Table 1). The limitations of these studies were their small sample sizes (N = 20–42), the main focus on good versus bad responders (not pCR), the univariate setting in which analyses were performed and the lack of validation. To increase the clinical applicability of these decision making tools, they need to be based on more evidence (i.e. larger number of patients and external validation), be trained on several data sources [29] and they require focus on outcomes that are more relevant in terms of decisions, like pCR for a possible wait-and-see policy. We hypothesize that models with these requirements are the most suitable for decision making in clinical practice. The aim of this study is therefore to develop an externally validated multivariate predictive model for pCR combining clinical, pre-treatment and intermediate FDG-PETCT imaging parameters based on a prospective study. After development of a nomogram and the evaluation of its accuracy, risk group definition based on these predictions may provide decision support to clinicians for LARC patients (Fig. 1).

Materials and methods

Study population

All data were prospectively collected (with written informed consent) between January 2007 and March 2012 within two institutes: MAASTRO Clinic (GROW, MUMC, Maastricht, The Netherlands) and Università Cattolica del S. Cuore (Rome, Italy). The following prospective observational studies were involved: a study (2007–2009) involving 47 patients from Maastricht [12,14], a pilot study (2007–2009) with 19 patients from Rome and a multicentre study (2009–2012) involving one protocol for both institutes (MAASTRO: 65 patients, Rome: 59 patients) with acronym THUNDER (THeragnostic Utilities for Neoplastic DisEases of the Rectum, NCT00969657). All patients from Maastricht were pooled and used to train a prediction model for pCR (N = 112). The pooled datasets from Rome were used for external validation of the model (N = 78). The study inclusion criteria were: histological proven rectal cancer (primary tumours), UICC stage I–III, no recurrences, only concurrent chemoradiotherapy treatment, minimal age of 18 years, and no previous radiotherapy to the pelvis. The available clinical variables used as candidate prognostic and predictive factors were age, gender, clinical tumour (cT) and nodal (cN) stage. The criteria followed to consider tumour nodal involvement at MRI were related to border contour (sharply demarcated or irregular border) and signal intensity characteristics (homogeneous or inhomogeneous) or size >8 mm [2,7]. All patients from Maastricht were treated preoperatively with radiotherapy (28 fractions of 1.8 Gy, 5 fractions/week) and concomitant chemotherapy (capecitabine, 825 mg/m^2, twice daily), followed by a total mesorectal excision 6–8 weeks after the end of CRT. A minority of the thunder patients (N = 11) with a clinical complete response (assessed using post-CRT MRI and endoscopy) were enrolled in a parallel study where a surgical wait-and-see policy was applied [20]. Some patients from Rome were also treated with 50.4 Gy schedule, but 78.2% of the patients were treated with 25 × 1.8 Gy schedule and a RT boost of 10 Gy. The majority of the Rome patients (N = 62) received a combination of capecitabine (1300 mg/m^2 daily) and oxaliplatin (60 mg/m^2 once a week for 5 weeks with 55.0 Gy RT or 130 mg/m^2 at 3 time points with 50.4 Gy RT), and the others capecitabine only (1650 mg/m^2 daily with 50.4 Gy RT or 1300 mg/m^2 daily with 55 Gy RT, N = 14) or raltitrexed (3 mg/m^2 at 3 time points, N = 2).

PETCT imaging

All patients underwent a pre-CRT PET scan (one week before the start of CRT) and an intermediate PET scan (two weeks after the start of CRT). All Maastricht PET-CT scans were performed by use of a dedicated Siemens Biograph 40 TruePoint PET-CT scanner (Siemens Medical, Erlangen, Germany). Rome scans were performed with a 3D GEMINI GXL PET-CT scanner with 16 slice CT (Philips Healthcare, Cleveland, OH). The PET acquisition settings were reported before and were calibrated for both institutes [14]. PET-based semi-automatic tumour contours were made by one observer using a dedicated software (TrueD, Siemens Medical, Erlangen, Germany). Contours were defined by a threshold for the standardized uptake-value (SUV) based on the tumour-to-background signal ratio, with the gluteus muscle as reference background [6,23]. From the resulting tumour contour, maximal tumour diameter (MaxDiam), metabolic tumour volume (MTV), and maximal and mean SUV values within the MTV were calculated. The same variables were scored for the intermediate CRT PET-CT scan and

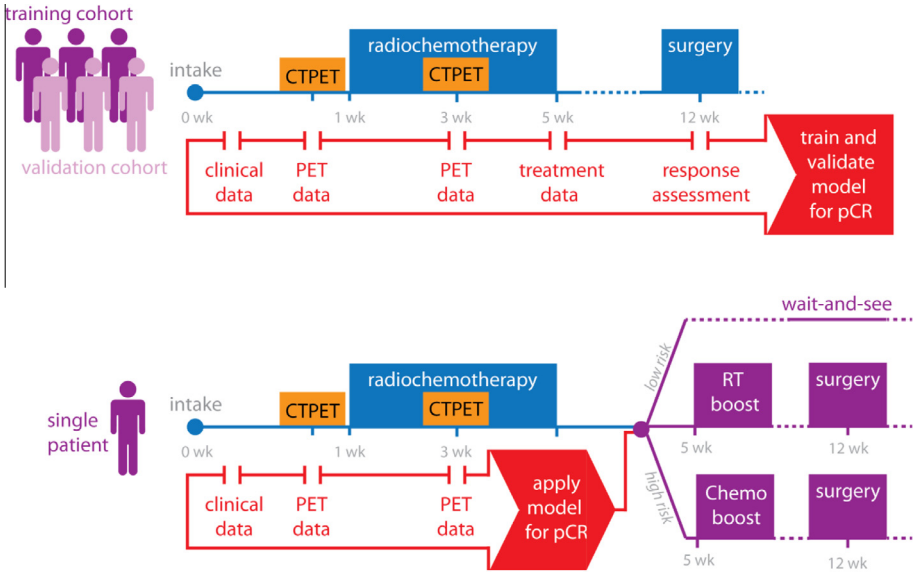

Fig. 1. Schematic overview of prediction model development (top) and the proposed application of the model in clinical practice after it has been tested in a clinical trial with a control arm (bottom).