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Prognostic value of tumor necrosis at CT in diffuse large B-cell lymphoma

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ABSTRACT

Objective: To determine the prognostic value of tumor necrosis at computed tomography (CT) in newly diagnosed diffuse large B-cell lymphoma (DLBCL).
Materials and methods: This retrospective study included 51 patients with newly diagnosed DLBCL who had undergone both unenhanced and intravenous contrast-enhanced CT before R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone) chemo-immunotherapy. Presence of tumor necrosis was visually and quantitatively assessed at CT. Associations between tumor necrosis status at CT and the National Comprehensive Cancer Network (NCCN) International Prognostic Index (IPI) factors were assessed. Cox regression analysis was used to determine the prognostic impact of NCCN-IPI scores and tumor necrosis status at CT.
Results: There were no correlations between tumor necrosis status at CT and the NCCN-IPI factors categorized age ($\rho = -0.042$, $P = 0.765$), categorized lactate dehydrogenase (LDH) ratio ($\rho = 0.201$, $P = 0.156$), extranodal disease in major organs ($\varphi = -0.245$, $P = 0.083$), Ann Arbor stage III/IV disease ($\varphi = -0.208$, $P = 0.141$), and Eastern Cooperative Oncology Group (ECOG) performance status ($\varphi = 0.015$, $P = 0.914$). In the multivariate Cox proportional hazards model, only tumor necrosis status at CT was an independent predictive factor of progression-free survival ($P = 0.003$) and overall survival ($P = 0.004$).
Conclusion: The findings of this study indicate the prognostic potential of tumor necrosis at CT in newly diagnosed DLBCL.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for 30–35% of cases [1]. Despite overall improvements in outcomes of DLBCL, particularly with the advent of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin and prednisolone) chemo-immunotherapy, approximately one-third of patients still develop relapsed/refractory disease that remains a major cause of morbidity and mortality [2]. Early identification of patients who will experience relapsed/refractory disease is of importance, because this will allow for the noninitiation or early discontinuation of ineffective standard front-line R-CHOP therapy, and provide a timely opportunity to switch to potentially more effective therapies. The International Prognostic Index (IPI) and its successors R-IPI and NCCN-IPI allow for risk stratification [3–5], but are insufficiently accurate to identify those patients in whom R-CHOP chemo-immunotherapy is likely going to fail. There is an active search for new prognostic biomarkers in DLBCL [1,2].

Imaging plays an important role in the evaluation of diffuse large B-cell lymphoma, and is done by means of computed tomography (CT), either as CT alone or in combination with ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET/CT) [6]. In the pretreatment setting, the main role of imaging is to detect and define the extent of disease for Ann Arbor staging and subsequent therapy response assessment. However, imaging findings may potentially also be useful to identify patients who are suffering from treatment-resistant DLBCL subtypes. CT scans of patients with

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DLBCL sometimes show tumor necrosis. Tumor necrosis shown at CT may indicate that the underlying DLBCL has an aggressive tumor growth. However, it is still unknown whether this phenomenon has any prognostic implications in DLBCL.

The purpose of this study was to determine the prognostic value of tumor necrosis at CT in newly diagnosed DLBCL patients who are treated with R-CHOP chemo-immunotherapy.

2. Materials and methods

2.1. Study design and patients

Local institutional review board approval was obtained for this retrospective study, and the requirement for written informed patient consent was waived. Any patient presenting with newly diagnosed DLBCL routinely undergoes pretreatment FDG-PET/CT at our institution. The hospital's database was searched for all patients with newly diagnosed DLBCL, who presented between September 2007 and December 2013. Inclusion criteria for this study were: newly diagnosed and histologically proven DLBCL, availability of both non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT from skull base to upper thigh as part of the same FDG-PET/CT examination that was performed on the same day, availability of blind bone marrow biopsy (BMB) of the posterior iliac crest and serum lactate dehydrogenase (LDH) measurement, and treatment with R-CHOP chemo-immunotherapy. Exclusion criteria for this study were: primary mediastinal DLBCL (which is recognized as a separate disease entity), previously treated/relapsed lymphoma, transformed lymphoma, coexistence of a second lymphoma subtype in the diagnostic biopsy, another cancer within the past five years, start of therapy before FDG-PET/CT.

2.2. Image acquisition

Non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT were acquired as part of an FDG-PET/CT examination, using a 40-detector row PET/CT system (Biograph 40 TruePoint PET/CT, Siemens Healthcare). Patients ingested a radio-opaque oral CT contrast agent (Telebrix Gastro, Guerbet) and fasted for 6 h before receiving 3 MBq/kg body weight of FDG intravenously. Sixty minutes after FDG injection, low-dose CT images from skull base to upper thigh were acquired using the following settings: 120 kV, 26–30 mAs (automatic dose modulation), 0.8-s tube rotation time, pitch of 1.2, and 1.5-mm slice width (reconstructed to contiguous 5-mm axial slices to match the slice thickness of the PET images). PET scanning was performed from mid femur to base of skull in five or six bed positions, with 3 min per bed position. Non-intravenous contrast-enhanced low-dose CT data were used for PET attenuation correction. PET images were reconstructed with an ordered-subsets expectation maximization algorithm for 14 subsets and four iterations. The image reconstruction matrix was 128 × 128. Finally, a non-ionic iodinated contrast agent (Xenetix 300, Guerbet; 3 mL/s with bolus tracking) was administered intravenously, and full-dose CT from skull base to midthigh was performed in the portal venous phase using the following settings: 120 kV, 60–160 mAs (automatic dose modulation), 0.8-second tube rotation time, pitch of 1.2, and 1.5-mm slice width.

2.3. Image interpretation

An experienced reader (T.C.K.) evaluated the combination of non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT for the presence of tumor necrosis. The reader was blinded to clinical and laboratory findings, findings of other imaging modalities, BMB findings, and patient outcome. Lymph nodes with a short-axis diameter exceeding 10 mm in the axial plane were considered positive for lymphoma. Any area of abnormal attenuation or mass in extranodal organs was also considered positive for lymphoma. Splenomegaly (i.e. splenic index exceeding 725 cm^3 [7]) was considered positive for lymphoma, but hepatomegaly without any focal liver lesions was not. Tumor necrosis was considered present if low-attenuation areas were visually identified in nodal or extranodal lymphomatous sites with corresponding Hounsfield units (HU) measuring between 10 and 30 Hounsfield units [8], and without any (relevant) HU increase (up to a maximum of 5 HU) between non-intravenous contrast-enhanced low-dose CT and intravenous contrast-enhanced full-dose CT images, as determined by region of interest analysis (ROI) (Figs. 1 and 2). Size-adjustable oval-shaped ROIs were used for this purpose. Sites of necrosis and corresponding HU values measured in the center of the necrotic area at intravenous contrast-enhanced full-dose CT were recorded.

2.4. National Comprehensive Cancer Network (NCCN) International Prognostic Index (IPI)

Age, serum LDH levels, presence of extranodal disease in major organs (either bone marrow, central nervous system, liver/gastrointestinal tract or lung), presence of Ann Arbor stage III/IV disease, and Eastern Cooperative Oncology Group (ECOG) performance status score of each patient were recorded, at time of diagnosis, in order to calculate an NCCN-IPI score, as described previously [5]. The four NCCN-IPI risk groups (low [scores 0–1], low-intermediate [scores 2–3], high-intermediate [scores 4–5] and high [scores 6–8]) were then dichotomized into low risk (including low and low-intermediate risk) and high risk (including high-intermediate and high risk) groups.

2.5. Patient follow-up

Clinical follow-up and follow-up FDG-PET/CT were used in all patients to determine if and when relapsed or progressive disease had occurred during follow-up, according to the Revised Response Criteria for Malignant Lymphoma [9]. Progression-free survival (PFS) was calculated from the date of diagnosis to documented disease relapse/progression or, for patients dying as a result of causes unrelated to DLBCL or the lymphoma treatment, the date of death. For surviving patients who did not experience disease relapse/progression, follow-up was censored at the date the patient was last known to be alive. Overall survival (OS) was calculated from the date of diagnosis until death as a result of any cause or, in surviving patients, censored at the date last known to be alive.

2.6. Statistical analysis

Associations between tumor necrosis status at CT (i.e. tumor necrosis absent or present) and the NCCN-IPI factors categorized age (>40–60, >60–75, and >75 years), categorized LDH ratio (>1–3 or ≥3 upper limit of normal), presence of extranodal disease in major organs (either bone marrow, central nervous system, liver/gastrointestinal tract or lung), presence of Ann Arbor stage III/IV disease, and ECOG performance status (≥2) were assessed using Spearman (ρ) (for ordinal NCCN-IPI factors) or Phi (φ) (for binary NCCN-IPI factors) correlation coefficient analyses.

PFS and OS were assessed using the Kaplan–Meier method with log-rank test [10], according to tumor necrosis status at CT (tumor