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Original article

Can clinicopathological parameters predict for lymph node metastases in ypT0-2 rectal carcinoma? Results of the CAO/ARO/AIO-94 and CAO/ARO/AIO-04 phase 3 trials

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ABSTRACT

Background: The advent of less radical surgical approaches has generated concern about leaving locoregional lymph node metastases (LNM) unresected that could lead to adverse outcome. We examined the prognostic role of clinicopathological factors for ypN-positivity in patients with ypT0-2 rectal carcinoma treated within the CAO/ARO/AIO-94 and CAO/ARO/AIO-04 randomized phase 3 trials.

Methods: The correlation of clinicopathological factors with ypN-status (ypN0 vs ypN1/2) was examined in $n = 776$ patients with ypT0-2 rectal carcinoma after preoperative CRT and total mesorectal excision surgery using Pearson's Chi-squared test for categorical variables and Kruskal–Wallis' test for continuous variables. Multivariable analysis was performed using binary logistic regression to identify independent prognosticators for ypN-positivity.

Results: Residual LNM (ypN+) were found in 6%, 20.8% and 21.4% of patients with ypT0, ypT1 and ypT2 carcinomas, respectively. Independent prognosticators for LNM were advanced ypT category ($p = 0.002$) and lymphatic invasion ($p = 0.020$). In a separate multivariable analysis performed upon exclusion of ypT-category due to multicollinearity with residual tumor diameter (RTD), lymphatic invasion ($p = 0.015$) and RTD $\geq$10 mm ($p = 0.005$) demonstrated strong correlation with LNM.

Conclusion: Advanced ypT-stage, lymphatic invasion and RTD $\geq$10 mm were prognostic factors for LNM in patients ypT0-2 rectal carcinoma treated with CRT and surgery within both phase 3 trials. The high incidence of LNM in the ypT1-2 group needs to be taken into consideration in the context of oncological safety and indicate that LE should be advocated with great caution in this patient subgroup. The prognostic pathological factor identified here could help guide decision of LE vs TME after standard CRT.

Neoadjuvant 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT), or short-course radiotherapy, followed by total mesorectal excision (TME) surgery is the standard treatment in locally advanced rectal cancer for a variety of endpoints, including local control, treatment compliance, and toxicity [1–3]. The quality of TME plane greatly determines local control as demonstrated in the MRC CR07 trial [4–7].

Radical TME is associated with early and late genitourinary and gastrointestinal morbidity that ranges between 15% and 50%, and adversely affects quality of life [8–10]. Hence, less radical approaches have been explored during the last decade. One option is local excision (LE) after CRT in low-lying T2 and early T3 tumors but is associated with variable local recurrence (LR) rates of 5%–15% [11–14]. An alternative option is the selective watch-and-wait non-operative management (NOM) introduced by Habr-Gama in rectal cancer patients with clinically complete response (cCR) after CRT, under the prerequisite of close follow-up [15–17]. This concept has gained significant attraction but, again, diverse LR rates (2–26%) have been reported, mainly endoluminal tumor regrowth [15,16,18–20].

The advent of less radical surgery has generated concern regarding the risk of leaving locoregional lymph node metastases

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(LNM) unresected in the mesorectum that could potentially lead to adverse prognosis. Indeed, despite the high sensitivity of MRI in the baseline setting for mesorectal facia and lymph node involvement [21], precise assessment of nodal status after preoperative CRT remains challenging [22]. Moreover, retrospective series have demonstrated variable LNM in patients with ypT0-2 tumors after preoperative treatment (ypT0: 1.8–17.4%; ypTis/T1: 7.0–20.8%; ypT2: 12.5–25.8%) that also correlated with high tumor grade and lymphatic invasion [23–30]. However, assessment of LNM in patients with ypT0-2 tumors treated with preoperative CRT within large phase 3 clinical trials is lacking. In the present post-hoc analysis, we assessed LNM in $n = 776$ patients with ypT0-2 rectal cancer treated as part of the CAO/ARO/AIO-94 and CAO/ARO/AIO-04 randomized phase 3 clinical trials [31,32] to identify clinicopathologic factors that predict for ypN-positivity.

Patients and methods

Study designs and participants

The design, eligibility criteria, treatment plan, follow-up and clinical outcome of both the CAO/ARO/AIO-94 and CAO/ARO/AIO-04 (ClinicalTrials.gov, NCT00349076) randomized phase 3 trials have been reported in detail before [1,31–33]. Both trials had received approval from the Ethics Committee, University of Erlangen, Germany. For the purpose of the present study, the clinical and pathologic characteristics of patients with ypT0-2 rectal carcinomas that received a complete resection (R0) were examined.

Histopathology analysis

Processing and analysis of the resected specimen has been described before [34,35]. The resected specimen was fixed in 4% formaldehyde overnight. All resection specimens were examined according to a standardized protocol, that included Union for International Cancer Control (UICC) TNM (fourth edition for CAO/ARO/AIO-94 trial; sixth edition for CAO/ARO/AIO-04 trial) categories and staging groups, the number of examined and involved lymph nodes, and the status of oral, aboral, and circumferential resection margins. For residual tumor, a minimum of 4 paraffin blocks were processed and an additional large area block was embedded. If no tumor was visible, the whole suspect (mostly fibrotic) area was sliced (5–8 mm thick slices) and embedded. Step section technique (three levels of the block) was used if no tumor was found on the first paraffin slide. For the determination of residual tumor, tissue samples were taken from the circumferential (lateral) surface, and also from the proximal and distal resection margins.

After opening of the resected specimen, the tumorous or fibrotic area was identified and described macroscopically. Tumor regression grade (TRG) was semiquantitatively (TRG categories: complete regression, TRG 4; intermediate regression, TRG 2/3; and poor regression, TRG 0/1) evaluated according to Dworak and colleagues [35–38]. Residual tumor diameter (RTD, in mm) was assessed measuring the maximal tumor expansion (longitudinal, transversal, sagittal) within the resection specimen. A cutoff 10 mm was used as reported [30].

Tumor margins were assessed by separation into three categories: well defined margins, diffuse infiltration into surrounding tissue and TRG category 4 (no tumor visible). The completeness of the resection was defined as R0 for negative margins (independent of the distance between tumor and resection margins), R1 for microscopic involvement, and R2 for gross residual tumor. Lymphoid aggregates as well as lymphatic, vascular and perineural invasion were also assessed.

Statistical analysis

The association of treatment arms (as received) and clinicopathologic characteristics with ypN-category (ypN0, ypN1 and ypN2) were assessed using Pearson's Chi-squared test for categorical variables and Kruskal–Wallis' test for continuous variables. Missing values were excluded before test performances. A $p < 0.05$ was considered as significant. Multivariable analysis was performed using binary logistic regression by including all parameters that showed significant association with LNM. The IBM SPSS® software, version 21 was used for statistical analysis.

Results

Patient selection

From the CAO/ARO/AIO-94 trial, 175 of 421 patients treated with preoperative CRT followed by TME had ypT0-2 carcinomas and were eligible for this analysis, whereas 601 of 1265 patients were included from the CAO/ARO/AIO-04 trial, resulting in a total of 776 patients with ypT0-2 rectal carcinomas from both trials.

Association of clinicopathologic parameters with lymph node metastases

The association of clinical characteristics, such as age, gender, tumor localization, cT- and cN-categories and type of chemotherapy with LNM is shown in Table 1. The median number of examined lymph nodes per patient in the entire cohort was 15 (range: 0–81, including patients with pCR). In total, 647 (83.4%), 111 (14.3%) and 18 (2.3%) patients presented with ypN0, ypN1 and ypN2-category, respectively. The median number of examined lymph nodes per patient was 15 (range: 0–81), 14 (range: 3–45) and 17 (range: 8–61) for in ypN0, ypN1 and ypN2, respectively ($p = 0.281$). We failed to detect a significant correlation for any of the clinical parameters with LNM (Table 1).

With regard to pathologic parameters (Table 2), LNM showed a significant correlation with advanced ypT category ($p < 0.001$), RTD $\geq$10 mm ($P < 0.001$), less advanced TRG ($p < 0.001$), high histological tumor grading G2/G3 ($P < 0.001$), venous invasion ($p = 0.009$) and lymphatic invasion ($p < 0.001$). We did not observe any significant association of LNM with the other factors (Table 2). There were no differences regarding rates of positive lymph nodes between the two trials (data not shown).

Pathological parameters with lymph node metastases according to ypT category

We examined the correlation of pathological parameters with LNM in the different ypT categories separately (Table 3 and Supplementary Table 1). In patients with ypT2 carcinomas after preoperative treatment ($n = 440$), LNM correlated significantly with TRG 0-1 ($p = 0.011$), venous invasion ($p = 0.044$) and lymphatic invasion ($p < 0.001$), whereas the other parameters failed to demonstrated any association with ypN (Table 3). In the ypT1-subgroup, only perineural invasion ($p < 0.001$) and lymphatic invasion ($p = 0.002$) showed significant correlation with advanced ypN category, whereas none of the parameters predicted for LNM in ypT0 tumors (Supplementary Table 1).

Multivariable analysis

Next, we conducted a multivariable analysis using binary logistic regression that included all factors found to correlate significantly with LNM in univariate analysis (Table 4). Advanced ypT-category (HR 21.85, 95% CI 1.26–2.72, $p = 0.002$) and presence

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