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Original article

Prophylactic irradiation of para-aortic lymph nodes for patients with locally advanced cervical cancers with and without high CA9 expression (KROG 07-01): A randomized, open-label, multicenter, phase 2 trial

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ABSTRACT

Background and purpose: The efficacy of prophylactic extended-field irradiation (EFI) plus concomitant cisplatin in patients with locally advanced uterine cervical cancer (LAUCC) is unknown, nor is it known whether tumor carbonic anhydrase IX (CA9) expression level, a hypoxia marker, influences survival outcome.

Material and methods: We recruited patients with UCC, FIGO stage IB1 with pelvic lymph node (LN) metastases to IVA with negative para-aortic LN on PET/CT. CA9 expression was examined and patients were randomized to either EFI or pelvic only radiotherapy (PRT) in each CA9 group. The primary outcomes were para-aortic recurrence-free survival (PARFS) and disease-free survival (DFS).

Results: Between 2006 and 2011, 79 patients with CA9-positive and 37 with CA9-negative tumors were enrolled, respectively. The median follow-up period was 69.2 months (range 6.8–102.1). For CA9-positive patients, 5-year PARFS was 100% and 81.7% for those receiving EFI and PRT ($p = 0.007$), respectively. DFS was 78.6% for EFI and 71.3% for PRT patients ($p = 0.353$). For CA9-negative patients, 5y PARFS was 100% and 94.1% for EFI and PRT ($p = 0.317$), respectively. DFS was 100% for EFI and 70.7% for PRT ($p = 0.018$).

Conclusion: EFI significantly reduced recurrences in PAN in patients with CA9-positive tumors, but survival outcome was not improved, due to high local recurrence and high distant metastases rates. This study indicates the necessity for new therapeutic strategies for LAUCC patients whose tumors show high CA9 expression.

Para-aortic lymph node (PAN) metastasis in patients with cervical cancer is an important determinant of prognosis [1]. Surgical LN staging in LAUCC shows 12–22% rate of occult PAN metastasis rate depending on pelvic LN positivity [2]. By surgical LN staging and [18F] fluorodeoxyglucose (FDG)-PET imaging, PAN metastasis was diagnosed in 20–60% of the patients with International Federation of Gynecology and Obstetrics (FIGO) stage II A-IVA, and the risk of disease recurrence was 6-fold higher than those who did not have metastasis [3]. Hence, prevention of PAN metastasis by EFI is considered as a strategy to increase the survival rate of patients with LAUCC. There were 3 large, multi-institutional clinical trials that evaluated the efficacy of prophylactic extended-field irradiation (EFI) in patients with LAUCC [4–6]. Among those, Radiation Therapy Oncology Group (RTOG) 79-20 found an overall survival gain of 10% in the EFI arm at 10 years' follow-up [6]. RTOG 90-01 which compared prophylactic EFI in a standard arm to pelvic only radiotherapy (PRT) combined with concurrent fluorouracil/cisplatin (FP) chemotherapy as a test arm showed better outcomes in the test arm [4]. However, neither EFI or PRT combined with FP chemotherapy has been seldom used as a standard treatment for LAUCC because of the 10% incidence of grade 4-5 late toxicity reported for both regimens [4,6].

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Tumor hypoxia has been found to be a strong prognostic factor in cervical cancer. Prior studies, including our own [7,8], have demonstrated that CA9 expression is highly associated with distant metastases, including PAN involvement. Yap et al. tried giving prophylactic para-aortic irradiation to the 73 selected patients with hypoxic tumors on the basis of Eppendorf measurement of pO_2, however, the study was performed in a non-randomized way and the result showed that there was no improvement in para-aortic recurrence free survival, disease-free survival, and overall survival rates compared with the 155 patients who did not receive prophylactic para-aortic irradiation [9]. The value of CA9 as a biomarker has neither been studied in a prospective fashion nor used as a means of treatment decisions in treatment of cervical cancer. Against this background, we designed a prospective randomized phase II trial for prophylactic para-aortic irradiation on the basis of hypoxia marker, CA9, to test whether concomitant cisplatin and EFI can reduce para-aortic recurrences and increase disease-free survival rate in LAUCC. Korean Radiation Oncology Group (KROG) 07-01, an open-label, prospective randomized phase II multi-institutional study, was designed to test whether prophylactic extended-field irradiation (EFI) to the PAN benefits patients with LAUCC relative to the hypoxic level of their tumors in terms of para-aortic recurrence-free survival (PARFS) and disease-free survival (DFS).

Materials and Methods

Eligibility

Pretreatment workup included MRI covering abdomen and pelvis and PET/CT with other routine work-up [10]. Eligibility criteria included (1) newly diagnosed, histologically confirmed squamous/adeno/adenosquamous carcinoma, (2) tumor at FIGO stage IB1 with pelvic LN metastasis, IB2, IIA, IIB, IIIA, or IIIB with only unilateral pelvic wall extension, (3) negative para-aortic lymphadenopathy determined by PET/CT scan and MRI, (4) adequate bone marrow and renal function, and (5) ECOG performance status of 0–2. The institutional review boards of all participating centers approved the study protocol, and all patients provided written informed consent. All patients' data were anonymized so as to protect the identities of subjects. This study was registered with ClinicalTrials.gov, with identifier number NCT00980759.

Sample size and study population

We considered the following when calculating sample size: the estimated risk of 5-year PAN recurrence rate was 25% and 15% for patients with CA9-positive and CA9-negative tumors, respectively [7], and the estimated EFI-induced risk for PAN metastasis to be <5% for both groups. Thus, 78 and 222 patients were needed for CA9-positive and CA9-negative group, respectively. With an estimated 10% follow-up loss, 330 patients were needed. Since the natural incidence ratio of patients with CA9-positive tumors to CA9-negative tumors was approximately 7:3 [7,8], and hence the enrollment would take much longer for the CA9-negative than the CA9-positive group, we planned to end the first phase of the study and report the result when enrollment of the CA9-positive group was complete and its follow-up period is over (part 1). In the second part, we enrolled the patients regardless of tumor CA9 expression and randomized the patients into EFI vs. PRT (part 2). The current study is the result of part 1.

Procedures

Tissues and CA9 immunohistochemical staining

CA9 staining was performed as previously described using M75 antibody [7]. CA9 expression was graded as 0 when $\leqslant$5% CA9 positivity was observed in the entire tumor area.

Chemoradiotherapy

We gave CT-based conformal external beam radiotherapy (EBRT) and high-dose–rate brachytherapy. The superior border was the L4-L5 inter-space for PRT and the T12-L1 inter-space for EFI. Radiation dose was 45–50.4 Gy/25–28 fractions for pelvic field depending on the FIGO stage and status of pelvic LN, and 45 Gy in 25 fractions for para-aortic field. High dose–rate brachytherapy was administered at 39.6–45 Gy, with six fractional 5-Gy doses given twice a week. Image-based 3D brachytherapy using CT or MRI was used in 90% of the patients. The total biological equivalent dose in 2-Gy fractions to Point A ranged from 72.3 to 102.2 Gy, with a median of 87 Gy. Median treatment duration was 58 days (inter-quartile range, 54–64 days). All patients received cisplatin at 40 mg/m^2 per week concomitant with radiotherapy, while 7 doses maximum was allowed.

Follow up, response evaluation, and evaluation of toxicity

Post-treatment follow-up policy and work-up studies were described previously [10]. The final primary tumor response was determined by physical examination, cervical cytology, and MRI at 3 month after radiotherapy. Patients were assessed for acute and late toxicity in accordance with RTOG acute radiation morbidity scoring criteria and RTOG/EORTC late radiation morbidity scoring criteria, respectively.

Outcome measurement

The primary end point for treatment comparison was 5-year PARFS rate and DFS rate. DFS was defined as survival without loco-regional recurrence, para-aortic recurrence, or distant progression. We considered persistent cervical diseases that did not regress for 2–3 months after completion of radiotherapy as local recurrences. We defined distant metastasis as recurrence outside the pelvis and para-aortic field. We defined cause-specific death as death attributable to the treated cancer or complications of the treatment. For disease event, we counted the first sites of recurrence as disease sites. We calculated all times from the date of study entry up to the date of relapse or the last date of follow-up. Deaths from other cause were censored at the time of last follow-up.

Statistical analysis

We included all assessable patients in the analysis except the 2 patients who had incomplete treatment. We used the Kaplan–Meier method for estimating PARFS, DFS, and overall survival (OS), the log-rank test for testing between-group survival differences, and the chi-square test to analyze the association between factors in the two groups. We used IBM SPSS for Windows, version 20.0, for statistical analysis and considered $p < 0.05$ significant.

Results

Patient distribution and characteristics

Between August 2006 and December 2011, the enrollment of planned 79 patients with CA9-positive tumors was completed. By this time, 37 patients with CA9-negative tumors were enrolled. One patient in CA9-positive/EFI group and one in CA9-negative/PRT group did not complete treatment and were lost to follow-up (Fig. 1). The median follow-up period was 69.2 months (range, 6.8–102.1) for all patients, and 74.8 months (range, 20.6–102.1) for surviving patients. Table 1 summarizes the patients' clinical characteristics. The CA9-positive and CA9-negative tumor groups did not differ significantly in clinical parameters, except that adenocarcinoma was more frequent in patients with CA9-negative tumors (Table 1).

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