Study Protocol

Topic: Evaluating the effectiveness of combining intensity-modulated radiotherapy technique and paclitaxel plus cisplatin chemotherapy into the treatment of high-risk inoperable cervical cancer.

Scientific title: Concurrent definitive chemoradiation incorporating intensity-modulated radiotherapy followed by adjuvant chemotherapy in high risk locally advanced cervical squamous cancer: A phase II study.

Study hypothesis: Incorporating both intensity-modulated radiotherapy and adjuvant chemotherapy into the concurrent definitive chemoradiation for patients with high risk locally advanced cervical squamous cancer might improve their survival.

Background and study aims: Cervical cancer is a type of cancer that occurs in the cells of the cervix - the lower part of the uterus that connects to the vagina. Radiation therapy (also called radiotherapy) is a cancer treatment that uses high doses of radiation to kill cancer cells and shrink tumors. In recent decades, intensity-modulated radiotherapy (IMRT) has become the mainstream treatment for patients with prostate, rectal, neck, and several other cancers. Such a technique allows for an escalated prescription dose to target areas while sparing normal tissues from excessive radiation. This study aims to recruit 50 patients to determine

whether the incorporation of the IMRT technique and adjuvant paclitaxel plus cisplatin chemotherapy would improve the survival of inoperable locally advanced cervical cancer. The goal is to find a more effective treatment strategy with less toxicity for this group of patients, and the study's findings should help to improve the well-being of patients who suffer from cervical cancer

Study design: Single-center interventional single-armed nonrandomized noncomparative phase II trial

Participants:

Patients would be enrolled if they meet following criteria:

1. Biopsy proven stage III-A- IV-A squamous cervical cancer or stage II-B disease with metastatic regional nodes.
2. Age 18-70 years
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1
4. No previous history of chemotherapy or radiotherapy
5. Sufficient bone marrow, including leukocyte count ≥4,000/mm^3, neutrocyte count ≥2,100 /mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥90 g/L.
6. Adequate renal and hepatic functions.
7. Normal cardiovascular function

Interventions:

Radiotherapy consists of intensity-modulated external-beam radiotherapy and brachytherapy. IMRT is delivered with dynamic multileaf collimators using 6 MV photon beams. Clinical target volume (CTV) is defined as the gross tumor plus areas potentially containing microscopic disease. The CTV is expanded by 5 mm uniformly to create the planning target volume (PTV). Prescription for PTV ranges from 45.0~50.0 Gy at 1.8 Gy~2.0 Gy/fraction in 25 fractions. Involved nodes are contoured separately and are defined as GTV nodes. A tailored margin of 3 mm is added to GTV nodes to generate PTV nodes, which are treated with a simultaneous integrated boost (SIB) technique to a total dose of 50.0–65 Gy at 2.0-2.6Gy/fraction in 25 fractions. Brachytherapy is initiated when 27.0~30.0 Gy of external beam is delivered to PTV. The aim of brachytherapy boost is to deliver cumulative EQD2 doses (combined external beam radiotherapy (EBRT) and brachytherapy delivered in 2 Gy equivalent doses) of ≥80 Gy to point A for stage B-A disease and ≥90 Gy for stage B-A disease. Specifically, a total dose of 28~35 Gy high-dose-rate (HDR) brachytherapy is prescribed to point A in 4~5 weekly fractions using an iridium-192 source. An additional fraction of 5-7 Gy brachytherapy will be delivered if a residual cervical tumor is suspected by pelvic examination or MRI. Chemotherapy consists of 4~6 cycles of concurrent cisplatin infusions and 2 cycles of adjuvant TP regimen. Concurrent weekly intravenous cisplatin at 30 mg/m² is initiated on the first day of radiotherapy for over 1 hour during EBRT. Adjuvant chemotherapy was scheduled within 4 weeks after the completion of CCRT and repeated 3 weeks later. Paclitaxel 150 mg/m^2 was given as

a 3-hour infusion on day 1, followed by cisplatin 35 mg/m^2 with a 1-hour infusion on days 1-2 (70 mg/m^2 in total). Discontinuation of chemotherapy is allowed in the event of grade 3-4 hematological or gastrointestinal toxicities. It will resume when patients' absolute neutrophil count recovers to ≥1500/mm^3 and their platelet count improves to ≥100,000/mm^3; however, doses of all agents should be subsequently reduced by 20%.

Statistical plan and power Calculation

Disease-free survival, loco-regional recurrence free survival, distant metastasis free survival, and overall survival was defined from the time of diagnosis to the time of first evidence of relapse or death from any cause. Patients without documented evidence of recurrence were censored at the date of last follow up visit. Cumulative survival rate was calculated with the Kaplan-Meier method using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Toxicities are reported as counts with percentages.

Possible benefits and risks of participating

Participants treated with such a technique might have improved outcomes. If such a treatment strategy is proven to be an effective option, it will influence how patients with inoperable cervical cancer will be treated in the future. In addition, part of the participants' examination and follow-up will be funded by the sponsor. The main risks for the participants may be the uncertainty of the superiority of such

a treatment plan over traditional treatment. That is, the treatment outcomes of the participants may not be superior to or may even be inferior to conventional CCRT. In addition, chemotherapy-related toxicities, including allergies, bone marrow suppression, hair loss, and liver or renal function impairment, might be another concern.

Study period

February 2010 to September 2017

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Ethics approval:

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