

学位論文内容の要旨

Chemoradiation as a definitive treatment for primary unknown cervical lymph node metastases.

(原発不明癌頸部リンパ節転移に対する根治的化学放射線療法)

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Aim: Cancers of unknown primary sites are defined as a heterogeneous group of metastatic tumors for which a standardized diagnostic work-up fails to identify the site of origin at the time of diagnosis. The optimal treatment for these patients remains unclear, as results from randomized comparative trials are lacking (Beldi et al., 2007). Although the optimal treatment is unclear, neck dissection followed by postoperative radiation seems to be the most widely accepted approach. Therefore, reports concerning the role of chemoradiation as a definitive treatment for CUP are limited. The purpose of this study was to assess the efficacy and toxicities of chemoradiation as the primary, definitive treatment for CUP, and to identify the factors which influence treatment outcomes.

Patients and Methods: Thirty consecutive patients who were diagnosed with CUP at our institutions from 1995 to 2012, and treated with chemoradiation as the primary treatment were included in the present study. Patients who were diagnosed with distant metastasis, or were followed-up for less than three months were excluded from the study. Twenty-three (77%) underwent PET or PET/CT before diagnosis. All patients had histologically confirmed malignant tumors, and 23 (77%) were squamous cell carcinomas. All patients were treated with curative intent. Radiotherapy (RT) was performed five days per week, with conventional fractionations (1.8-2 Gy per fraction). The median total dose was 70.2 Gy (range=43.2-74.2 Gy). The median total treatment period was 57 days (range=38-74 days). X-Ray irradiation of 4-15 MV were used for all cases, and 6-11 MeV electrons were used for radiation boost in 21 (70%) cases. All patients received RT to the bilateral neck, including the pharyngeal axis. All 30 patients received chemotherapy, and most of them (29/30, 97%) concurrently. As concurrent chemotherapy, 15 patients received a cisplatin- and 5-fluorouracil based regimen. The remaining 14 patients received a platinum-based agent alone, or 5-fluorouracil alone. As neoadjuvant or adjuvant chemotherapy, 5-fluorouracil was administered in most cases. All actuarial survival and control rates were calculated using the Kaplan-Meier method. Overall survival (OS) was defined as death from any cause. Disease-free survival (DFS) was defined as the time to the first treatment failure, and locoregional control (LRC) was defined as the time to the first in-field relapse. Toxicities were

described by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Log-rank test was used for univariate analysis to identify prognostic factors which predicted treatment outcomes.

Results: After the initial treatment, 16 patients (53%) showed complete response, whereas 12 (40%) had progressive disease, and two (7%) stable disease. After a median follow-up of 25 months (range=7-91 months) for surviving patients, the two and five-year LRC rates were 56% and 45%, respectively. Disease recurrences were observed in 18 (60%) patients after the primary treatment. The recurrences presented inside the radiation field in 15 patients (50% of the whole cohort, 83% of all recurrences), and as distant metastases in five patients (17% of the whole cohort, 28% of all recurrences). Both in-field relapse and distant metastases were seen in three (10%) patients. Among the in-field relapses, twelve were LN metastases, two were emergence of the primary tumor, and one had both. Five patients received salvage surgery after the primary treatment. Four patients received salvage surgery for residual or recurrent tumors inside the radiation field. Three patients received re-irradiation to the neck. Emergence of the primary tumor after the treatment was observed in four (13.3%) cases. The lesions were located at the base of tongue, hypopharynx, thyroid, and maxillary sinus, respectively. The 2-year/5-year OS and DFS rates were 69%/52%, and 46%/36%, respectively. Twelve deaths were recorded; 11 out of the 12 patients died from disease progression, one patient died from lung cancer, which was not related to the cervical lesion. The median OS was 85 months. Univariate analysis identified no factor that significantly affected OS. PS was significantly associated with DFS ($p=0.001$). In addition, patients with metastatic lesions limited to level 2 or 3 LN areas exhibited a significantly better DFS rate compared to those with involvement of other areas ($p=0.009$). PS was also significantly associated with LRC ($p=0.002$). Treatment-related deaths did not occur. All acute toxicities were manageable and temporary. No late toxicity greater than grade 3 was observed.

Discussion: The treatment outcomes of CUP treated with definitive chemoradiation were in line with previously reported studies which included patients who underwent surgery and postoperative RT (Fakhrian et al., 2012). However, locoregional relapses were common, requiring improvement in LRC. Toxicities were acceptable and well-tolerated. Several prognostic factors, including metastases limited to level 2 or 3 LNs as a newly suggested factor, were implied. Larger clinical studies to validate these results are warranted.

References:

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論文目録

I 主論文

Chemoradiation as a definitive treatment for primary unknown cervical lymph node metastases.

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