pISSN 1598-2998, eISSN 2005-9256

Cancer Res Treat. 2016;48(3):907-916 http://dx.doi.org/10.4143/crt.2015.359

Original Article Open Access

The Effect of Induction Chemotherapy Using Docetaxel, Cisplatin, and Fluorouracil on Survival in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Meta-Analysis

Ryul Kim, MD[1], **Seokyung Hahn,** PhD[2,3], **Junghoon Shin,** MD[1], **Chan-Young Ock,** MD[1], **Miso Kim,** MD[1], **Bhumsuk Keam,** MD, PhD[1,4], **Tae Min Kim,** MD, PhD[1,4], **Dong-Wan Kim,** MD, PhD[1,4], **Dae Seog Heo,** MD, PhD[1,4]

[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, [2]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, [3]Department of Medicine, Seoul National University College of Medicine, Seoul, [4]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

Supplementary Data

Table of Contents

Supplementary Table 1. Initial search strategies performed in April 2015

Database	Syntax	Retrieval
Pubmed	(((((head[Title/Abstract] AND neck[Title/Abstract])) AND ((cancer[Title/Abstract]) OR carcinoma[Title/Abstract]))) AND induction[Title/Abstract]) AND randomi*[Title/Abstract]	174
EMBASE	TITLE-ABSTR-KEY("head and neck") and TITLE-ABSTR-KEY(cancer OR carcinoma) and TITLE-ABSTR-KEY(induction) and TITLE-ABSTR-KEY(randomi*)	47
Cochrane	head and neck in Title, Abstract, Keywords and induction in Title, Abstract, Keywords and randomi* in Title, Abstract, Keywords and (cancer OR carcinoma)	157
National Institutes of Health Clinical Trials Registry	"head and neck" AND (cancer OR carcinoma) AND induction	369
MetaRegister of controlled clinical trials	"head and neck" AND (cancer OR carcinoma) AND induction	9

Supplementary Table 2. Treatment protocols of each study included in the meta-analysis

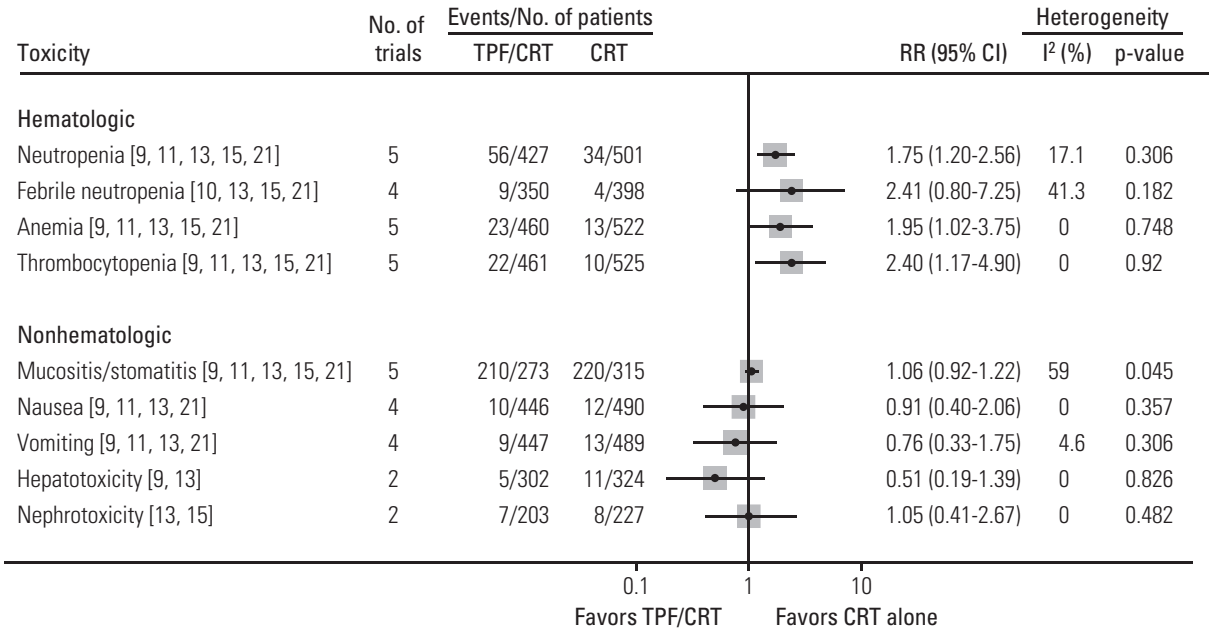
Treatment		Haddad et al. [10]	Cohen et al. [9]	Paccagnella et al. [22]	Hitt et al. [11]	Ghi et al. [13]	Takacsi-Nagy et al.[15]
TPF	Docetaxel	75 mg/m^2 IV on D1	75 mg/m^2 IV on D1	75 mg/m^2 on D1	75 mg/m^2 on D1	75 mg/m^2 on D1	75 mg/m^2
	Cisplatin	100 mg/m^2 IV on D1	75 mg/m^2 IV on D1	80 mg/m^2 on D1	75 mg/m^2 on D1	80 mg/m^2 on D1	75 mg/m^2
	5-FU	1,000 mg/m^2/day CIV on D1-4	750 mg/m^2/day CIV on D1-4	800 mg/m^2/day CIV on D1-4	750 mg/m^2/day on D1-5	800 mg/m^2/day on D1-4	750 mg/m^2/day on D1-4
	Cycles	Every 3 wk for 3 cycles	Every 3 wk for 2 cycles	Every 3 wk for 3 cycles	Every 3 wk for 3 cycles	Every 3 wk for 3 cycles	Every 3 wk for 2 cycles
	Prophylactic G-CSF	Allowed	Allowed	Not allowed	Allowed		Not allowed
CRT	Chemotherapy	Docetaxel 20 mg/m^2 weekly for 4 wk[a] or carboplatin AUC 1.5 weekly for 7 wk[a] or cisplatin 100 mg/m^2 on D1, D22[a]	Hydroxyurea 500 mg PO twice daily for 6 days and 5-FU 600 mg/m^2/day CIV for 5 days and docetaxel starting at 20 mg/m^2 on D1 and increased by 5 mg/m^2 in successive dose levels (maximum 30 mg/m^2)	Cisplatin 20 mg/m^2/day IV D1-4 and 5-FU 800 mg/m^2/day IV over 96 hr during weeks 1 and 6 of RT	Cisplatin 100 mg/m^2 on D1, D22, D43	Cisplatin 20 mg/m^2 on D1-4 and 5-FU 800 mg/m^2/day CIV over 96 hr on weeks 1 and 6[b] or cetuximab 400 mg/m^2 as first dose 7 days before the beginning of radiotherapy; subsequent doses 250mg/m^2 were administered, weekly, for 7 times	Cisplatin 100 mg/m^2 D1, D22, D43 of RT
	Radiotherapy	Accelerated concomitant boost given 5 days a week over 6 or 7 wk (total dose 72 Gy in 1.8/1.5 Gy fractions or 70 Gy in 2.0 Gy fractions)	Twice daily 3-D conformal RT or IMRT (total dose 74 to 75 Gy to gross, 54 Gy to high-risk microscopic, and 39 Gy to low-risk microscopic disease)	Standard fractionated RT of 70 Gy for the primary tumor (2 Gy/day, 5 days/wk for 7 wk) and RT of ≥ 60 Gy for the neck (2 Gy/day, 5 days/wk for 5 wk)	Conventional fractionation in a 1.8-2.0 Gy once daily fraction, 5 days/wk until the total tumor dose of 70 Gy, and 50 Gy in the lymph node areas with microscopic disease	Conventional RT for 2 weeks (total 70 Gy, 2 Gy/day, 5 days/wk)	The planned radiation dose to the primary tumor and the involved lymph nodes was 70 Gy (2 Gy/day, 5 days/wk) and 50 Gy to the lymph node areas with microscopic disease; all patients were irradiated using the ConPas technique

TPF, docetaxel-cisplatin-fluorouracil; IV, intravenous infusion; D, day; 5-FU, fluorouracil; CIV, continuous intravenous infusion; G-CSF, granulocyte colony-stimulating factor; CRT, concurrent chemoradiotherapy; AUC, area under curve; PO, orally; RT, radiotherapy; 3-D, three-dimensional; IMRT, intensity-modulated radiation therapy; ConPas, conformal parotid-sparing technique. [a]After 3 cycles of induction chemotherapy, patients were stratified by response to receiving more or less intensive chemoradiotherapy, [b]Patients assigned to the TPF/CRT arm were further randomly assigned to receive either cisplatin/5-FU or cetuximab for CRT.

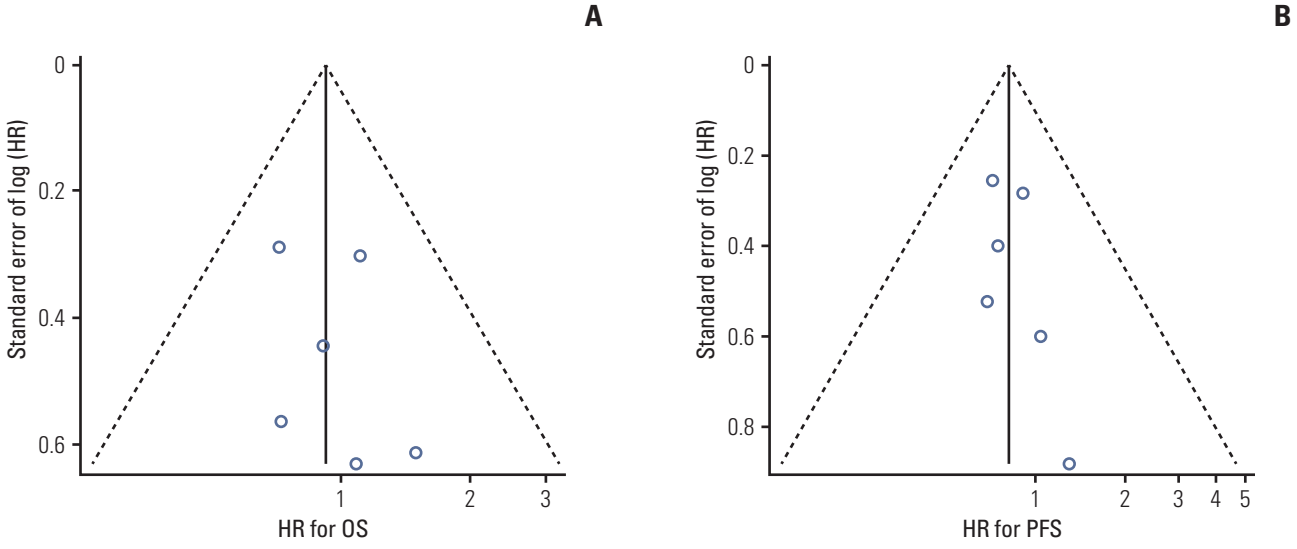
Supplementary Table 3. Methodological assessments of studies included in the meta-analysis using Cochrane Collaboration's tool

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting
Haddad et al. (2013) [10][a]	Low (minimization)	Low (central allocation)	High	Low	Low
Cohen et al. (2014) [9][a]	Low (permuted-block)	Unclear	High	Low	Low
Paccagnella et al. (2010) [22]	Unclear	Low (central allocation)	High	Low	Low
Hitt et al. (2014) [11]	Unclear	Low (central allocation)	High	Low	Low
Ghi et al. (2014) [13][b]	Unclear	Unclear	High	Unclear	Unclear
Takacsi-Nagy et al. (2015) [15][a]	Low	Unclear	High	Low	Low

[a]These studies were prematurely terminated because of slow accrual, [b]These trials have not yet been published.



Supplementary Fig. S1. Relative risks for grade 3-4 adverse events from the trials with available data. TPF, docetaxel-cisplatin-fluorouracil; CRT, concurrent chemoradiotherapy; RR, relative risk; CI, confidence interval.



Supplementary Fig. S2. Funnel plots comparing HRs for OS (A) and PFS (B). HR, hazard ratio; OS, overall survival; PFS, progression-free survival.