



Title	Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma
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Preliminary Results of NPC-0501 Trial to Evaluate the Therapeutic Gain by Changing Chemoradiotherapy from Concurrent-Adjuvant to Induction-Concurrent Sequence, Radiotherapy from Conventional to Accelerated Fractionation, and Fluorouracil to Capecitabine for Locoregionally Advanced Nasopharyngeal Carcinoma

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Keywords:	nasopharyngeal carcinoma, randomized controlled trial, chemoradiotherapy, capecitabine, accelerated fractionation

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4 **Original Article**
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9 **Preliminary Results of NPC-0501 Trial to Evaluate the Therapeutic Gain by Changing**
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11 **Chemoradiotherapy Sequence from Concurrent-Adjuvant to Induction-Concurrent,**
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13 **Fluorouracil to Capecitabine, and Radiotherapy Fractionation from Conventional to**
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15 **Accelerated for Locoregionally Advanced Nasopharyngeal Carcinoma**
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47 48 49 **CONFLICT OF INTEREST DISCLOSURES**

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52 None of the authors have any potential conflict of interest.
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12
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14
15 statistical analyses are appropriate, and colleagues of all participating centers for their
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17 contribution.
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21 22 23 24 25 PRECIS

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27 Preliminary results from NPC-0501 Trial showed that the benefit of changing from
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29 concurrent-adjuvant to induction-concurrent sequence remains uncertain; replacing
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31 fluorouracil by capecitabine warrants further validation in view of convenience, favorable
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33 toxicity profile and at least comparable efficacy. In concurrence with studies on other head
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35 and neck cancers, accelerated fractionation is not recommended for locoregionally advanced
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41 nasopharyngeal carcinoma treated by chemoradiotherapy.
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4 **BACKGROUND:** A current recommendation for locoregionally advanced nasopharyngeal
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6 carcinoma (NPC) is conventional-fractionated radiotherapy with concurrent cisplatin plus
7
8 adjuvant cisplatin and fluorouracil (PF). This randomized trial evaluates the therapeutic
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10 benefit by changing to induction-concurrent sequence, oral capecitabine (X) and/or
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12 accelerated fractionation. **METHODS:** Patients with stage III-IVB non-keratinizing NPC
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14 were randomly allocated to one of six arms. The protocol was amended in 2009 to permit
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16 confining randomization to conventional-fractionated arms. The primary endpoint was
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18 progression-free survival (PFS); secondary endpoints included overall survival and safety.
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24 **RESULTS:** A total of 803 patients were accrued (706 randomly allocated to all six arms).
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26 Comparisons of Induction-PF vs adjuvant-PF did not show significant improvement.
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28 Unadjusted comparisons of Induction-PX vs adjuvant-PF showed favorable trend in PFS in
29
30 the Conventional-fractionated stratum ($P = .045$); analyses adjusted for other significant
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32 factors and fractionation showed significant reduction of progression (hazard ratio 0.54
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34 [0.36-0.80]) and death (0.42 [0.25-0.70]). Unadjusted comparisons of Induction vs Adjuvant
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36 sequence did not reach statistical significance, but adjusted comparisons showed favorable
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38 improvement. Comparisons of Induction-PX versus Induction-PF showed less toxicities
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40 (neutropenia and electrolyte disturbance), unadjusted comparisons of efficacy were
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42 statistically insignificant, but adjusted analyses showed lower hazard of death (0.57
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44 [0.34-0.97]). Changing fractionation from Conventional to Accelerated did not achieve any
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46 benefit, but incurred higher toxicities (acute mucositis and dehydration). **CONCLUSIONS:**
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48 Preliminary results showed that the benefit of changing to induction-concurrent sequence
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4 remains uncertain; replacing fluorouracil with oral capecitabine warrants further validation;
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6 accelerated fractionation is not recommended for locoregionally advanced NPC treated with
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9 chemoradiotherapy.
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14 **KEYWORDS:** nasopharyngeal carcinoma, randomized controlled trial, chemoradiotherapy,
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16 capecitabine, accelerated fractionation
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INTRODUCTION

Since the first report of significant survival benefits by the Intergroup-0099 Study,¹ addition of concurrent cisplatin plus adjuvant cisplatin and fluorouracil (PF) to conventional-fractionated radiotherapy (RT) has become a standard recommendation in National Comprehensive Cancer Network (NCCN) practice guideline² for patients with locoregionally advanced nasopharyngeal carcinoma (NPC). Three subsequent trials confirmed the efficacy of this concurrent-adjuvant strategy.³⁻⁵ However, distant control remains a key problem, more efficacious regimen is needed.

The Hong Kong Nasopharyngeal Cancer Study Group initiated this multi-center randomized controlled trial to evaluate three promising strategies. The first strategy is to change the chemotherapy sequence from concurrent-adjuvant to induction-concurrent. An exploratory study⁶ based on patients from the NPC-9901⁴ and NPC-9902⁷ Trials showed that the number of adjuvant cycles and the dose of fluorouracil given had significant impact on distant control. However, the adjuvant phase is often poorly tolerated. Changing to induction, with better tolerance⁸ and upfront use of cytotoxic drug combination, could theoretically be more effective for eradicating potent micro-metastases. In addition, this could shrink the primary tumor to give wider margin for RT, an advantage that is particularly needed for tumors infiltrating/abutting critical neurological structures.⁸ With encouraging results extensively reported from Phase II studies since the first report by Rischin et al,⁹ this has been included as an option (Category 3 evidence) in NCCN guideline² and (II, B evidence) in European guideline.¹⁰

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4 Our second strategy is to improve the current PF regimen by replacing fluorouracil
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6 (given by infusion) with capecitabine (Xeloda, oral preparation manufactured by Roche).
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8 Besides obvious advantage of convenience,¹¹ potential improvement in efficacy and
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10 safety¹²⁻¹⁵ could be achieved because capecitabine is metabolized to fluorouracil via a
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12 three-step enzymatic cascade with final conversion mediated by thymidine phosphorylase, an
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14 enzyme present at significantly increased concentrations in a wide range of solid tumors
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16 compared with normal tissue; furthermore, uracil analogues may have anti-angiogenic
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18 effect.¹⁶
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25 NPC-9902 Trial⁷ suggested that combining concurrent-adjuvant chemotherapy with
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27 accelerated fractionation could improve tumor control for advanced local diseases. However,
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29 this can only be taken as hypothesis-generating because the trial was terminated early due to
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31 slow accrual. Our third strategy is to re-evaluate the potential benefit by changing RT
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33 fractionation from conventional to acceleration.
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40 MATERIALS AND METHODS

41 *Patients*

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43 Eligible patients had histologically confirmed non-keratinizing (differentiated or
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45 undifferentiated) NPC by World Health Organization Classification; Stage III-IVB (tumor
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47 with bony structure, paranasal sinuses [T3], or intracranial extension, cranial nerve,
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49 hypopharynx, orbit, infratemporal fossa (masticator space) involvement [T4]; cervical lymph
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51 node metastasis with bilateral involvement [N2], greatest dimension >6 cm [N3a] or
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3 extension into supraclavicular fossa [N3b]; and no distant metastasis [M0]) by American
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6 Joint Committee on Cancer Staging System (6th edition).¹⁶ Other inclusion criteria were age
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9 18-69 years, performance status of 2 or lower by the Eastern Cooperative Oncology Group
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11 System, adequate hematologic and renal functions. The exclusion criteria were pregnancy or
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13 lactation, history of previous treatment, or prior malignancy.
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17 The protocol was approved by the institutional ethics committees of individual
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19 participating center, and the trial was monitored by an independent Data Monitoring
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21 Committee. All patients provided written informed consent.
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24 All patients were assessed by complete physical examination, fiberoptic
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26 nasopharyngoscopy, magnetic resonance imaging and/or computed tomography of the
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28 nasopharyngeal region, chest radiograph, complete blood count, renal and liver function tests,
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30 and lactate dehydrogenase (LDH). Additional investigations were performed for those with
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32 suspicious findings or abnormal biochemical profile.
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40 ***Study Design and Randomization***

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42 Eligible patients were stratified by participating center and stage (III vs IV), and randomly
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44 allocated in equal proportions to six arms. Blocks of variable size were chosen randomly by
45
46 the designing statistician to ensure both randomness and investigator blinding; sealed
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48 envelopes for each stratum (defined by center and stage) were sequentially numerated and
49
50 sent to the randomization office in each center, where patient eligibility is confirmed and the
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52 sealed envelope with the next number in the corresponding stratum is opened to allocate
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4 treatment.

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6 In accordance with the original protocol (September 2006), eligible patients were
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8 initially randomized in equal proportions to one of the six arms (Fig. 1). The protocol was
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10 amended in January 2009 following the recommendation of the independent Data Monitoring
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12 Committee: individual centers with logistical difficulty to arrange six RT fractions per week
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14 were allowed to opt out of the accelerated fractionation portion of the trial in order to
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16 improve accrual.
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22 The protocol specified two reporting: a preliminary report after the closure of the
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24 study (regardless of their significance) and the final report after 5-year follow-up for all
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26 surviving patients.
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32 ***Treatment and Assessment***

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34 Patients in all arms were irradiated with megavoltage photons using the same RT technique
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36 and dose in line with the policy of individual center. A total dose of 70 Gy or greater (66 Gy
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38 for T1-2a) was given to the gross tumor targets, and 50 Gy or greater to potential sites of
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40 local infiltration and bilateral cervical lymphatics. Additional boosts (not exceeding 20 Gy)
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42 could be given to the parapharyngeal space, the primary or nodal sites (when indicated); the
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44 boost field was confined to the involved site with exclusion of critical structures. The number
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46 of fractions per week was 5 in the Conventional group, and 6 in the Accelerated group (the
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48 sixth fraction was given either on Saturday or on a weekday with ≥ 6 hours between
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50 fractions).
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4 Patients in all arms were given concurrent cisplatin 100 mg/m² intravenous infusion
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6 (IVI) every 21 days for 2-3 cycles (depending on overall RT time). Patients allocated to the
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8 Adjuvant-PF group were given adjuvant cisplatin 80 mg/m² IVI + fluorouracil 1000
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10 mg/m²/day IVI for 96 hours every 28 days for 3 cycles. Patients allocated to the Induction-PF
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12 group were given induction cisplatin 100 mg/m² IVI + fluorouracil 1000 mg/m²/day IVI for
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14 120 hours every 21 days for 3 cycles. For patients allocated to the Induction-PX group,
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16 fluorouracil was replaced by capecitabine 2000 mg/m²/day orally for 14 days per cycle. Dose
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18 modifications were permitted according to protocol-specified criteria.
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25 The intended total dose of chemotherapy per treatment arms are as follows:

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27 Arm 1A: Cisplatin 540mg/m², 5-Fluorouracil 12,000 mg/m²

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29 Arm 1B: Cisplatin 440mg/m², 5-Fluorouracil 12,000 mg/m²

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31 Arm 2A: Cisplatin 600mg/m², 5-Fluorouracil 15,000 mg/m²

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33 Arm 2B: Cisplatin 500mg/m², 5-Fluorouracil 15,000 mg/m²

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35 Arm 3A : Cisplatin 600mg/m², Capecitabine 84,000 mg/m²

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37 Arm 3B : Cisplatin 500mg/m², Capecitabine 84,000 mg/m²

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43 The first assessment of tumor response was performed 6 weeks to 16 weeks after
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45 completion of RT. All patients were assessed by complete physical examination and
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47 fiberoptic nasopharyngoscopy. Further investigations with computed tomography/MRI or
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49 other tests were arranged when indicated (regular imaging assessment was not routinely
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51 performed due to limitation of resources). Persistent primary or nodal disease at 16 weeks
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60 after completion of RT was taken as locoregional failure. Persistent disease and relapse were

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4 treated with the policy of individual center. Common Toxicity Criteria for Adverse Events
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6 version 3.0 was used to gauge toxicities (both acute and late).
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10 11 *Statistical Analysis* 12

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14 All analyses were performed on an intent-to-treat basis, the tests are two-sided, and events for
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16 actuarial rates were measured from the date of randomization as the starting date. For the
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18 preliminary report, the primary endpoint is progression-free survival (PFS, time to first
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20 failure at any site or death due to any cause). The standard group is the Adjuvant-PF group
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22 with Conventional-fractionated RT, 5-year results were estimated from previous reports.^{4,5,7,18}
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27 The following sets of hypotheses and assumptions are used for power calculation:
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30 H0: The null hypotheses of no difference in treatment efficacy: 5-year PFS is 65% in all
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32 groups;
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35 HA: The alternative hypotheses of treatment efficacy: the 5-year PFS is 65% in the
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37 standard group and 75% in the experimental groups.
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40 For detecting this 10% difference in PFS with alpha error of 0.05 and 80% power, the target
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42 accrual is 798 patients.
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46 Secondary endpoints for treatment efficacy in the preliminary report included overall
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48 survival (OS, time to death due to any cause). Secondary endpoints for safety included major
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50 toxicities (grade 3 or above) both acute (incidence rates compared by Chi-square) and late
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52 (time to toxicities compared by log-rank test).
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56 Primary comparisons include comparisons of each induction regimen to the adjuvant
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4 regimen (Induction-PF vs Adjuvant-PF, Induction-PX vs Adjuvant-PF) and fractionation
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6 (Accelerated vs Conventional). Secondary comparisons include comparisons of sequence
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8 (Induction vs Adjuvant) and induction regimens (Induction-PX vs Induction-PF group).
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11 Stratified log-rank test was used: comparisons on regimen groups and sequence were
12 stratified by fractionation (Accelerated, Conventional), while comparisons on fractionation
13 were stratified by regimen groups (Adjuvant-PF, Induction-PF, Induction-PX). In addition,
14 multivariate analyses by Cox regression were performed to evaluate independent significance
15 of intervention and other potential prognostic factors.
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27 **RESULTS**

28 *Basic Characteristics and Radiotherapy*

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30 From September 2006 to 2012, 803 eligible patients from seven participating centers were
31 randomly allocated (Fig 1): 706 patients were randomly allocated to all six arms and 97
32 patients to Conventional-fractionated arms only. All except one patient with lost record were
33 analyzed.
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43 The six treatment arms were well balanced in all patient characteristics, tumor factors,
44 RT technique and total dose (Table 1). The median duration of follow-up for the whole series
45 was 3.3 years (range 0.1-7.1).
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51 *Chemotherapy Tolerance*

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56 The number of concurrent cycles varied with both chemotherapy sequence and fractionation
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4 (Table 2). As the mean overall RT time for the Accelerated group was shorter than the
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6 Conventional group (mean 40 vs 47 days), the proportion of patients with 3 concurrent cycles
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8 was correspondingly lower (11% vs 43%, $P < .001$), but the proportion with at least 2
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10 concurrent cycles was identical (92% in both). Significantly higher proportion of patients in
11
12 the Induction group completed 3 non-concurrent cycles as compared with the Adjuvant group
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14 (88% vs 64%, $P < .001$), but lower proportion had ≥ 2 concurrent cycles (90% vs 95%, P
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16 = .009). There were no significant differences between the two induction regimens (PX vs PF)
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18 in the mean number of cycles given during both phases ($P > .47$).
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27 *Efficacy*

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30 In this preliminary study, the core analyses on efficacy were based on the 706 patients
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32 randomized to all six arms as planned in the original study design: 171 patients had
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34 progression (failure or death) and 116 had death due to any cause. Table 3 summarized the
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36 comparisons of PFS and OS rates by stratified log-rank test; Fig. 2-3 showed the actuarial
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38 PFS curves for each stratum. Univariate analyses showed significant impact by other factors
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40 (including stage, LDH, age, sex, RT technique and center), the independent effect of
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42 intervention methods were analyzed by Cox regression with adjustment for these factors
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44 (Table 4).
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51 Comparisons of regimen Induction-PF vs Adjuvant-PF did not show statistically
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53 significant improvement. Unadjusted comparisons of Induction-PX vs Adjuvant-PF showed
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55 favorable trend in PFS in the Conventional stratum (Fig. 2A, 81% vs 75% at 3-year, $P = .045$),
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4 but insignificant differences in the Accelerated stratum. When adjusted for other significant
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6 factors and fractionation, Induction-PX achieved significant reduction in hazard of
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8 progression (hazard ratio [HR] 0.54, [95% confidence interval 0.36-0.80], $P = .002$) and
9
10 death (HR 0.42 [0.25-0.70], $P = .001$). When the two induction regimens were combined for
11
12 evaluation of Induction vs Adjuvant sequence, unadjusted comparisons did not reach
13
14 statistical significance, but adjusted comparisons showed reduction in hazard of progression
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16 (HR 0.67, [0.48-0.93], $P = .016$) and death (HR 0.57 [0.39-0.86], $P = .006$).
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22 For comparisons of capecitabine vs fluorouracil, unadjusted comparisons of
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24 Induction-PX vs Induction-PF did not show significant improvement, but adjusted analyses
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26 showed lower hazard of death (HR 0.57 [0.34-0.97], $P = .037$). Finally, all comparisons (both
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28 adjusted and unadjusted) of fractionation Accelerated vs Conventional did not show any
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30 benefit.
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38 *Safety*

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40 Table 5 summarizes major toxicities grade 3 or above. The Induction group had higher
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42 incidence of chemotherapy-related toxicities including neutropenia, thrombocytopenia, renal
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44 impairment and peripheral neuropathy, but less weight loss than the Adjuvant group.
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46 Comparison of the two induction regimens showed that induction-PX had less neutropenia
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48 and electrolyte disturbance. The Accelerated group had significantly higher incidence of
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50 acute mucositis and dehydration than the Conventional group.
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56 Majorities of toxicities are uneventful; treatment mortality for the whole series was
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4 1.2%. There were no significant differences in late toxicities and non-cancer deaths among
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6 the groups.
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11 **DISCUSSION**

14 There is little controversy that addition of chemotherapy could achieve significant survival
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16 benefit for patients with locoregionally advanced NPC, and concurrent sequence is the most
17
18 efficacious for combining with RT.¹⁹ There are differences of opinion as to whether
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20 concurrent alone or concurrent-adjuvant chemotherapy should be recommended. Preliminary
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22 results from a randomized trial by Chen et al.²⁰ comparing concurrent-adjuvant vs concurrent
23
24 alone chemoradiotherapy showed no statistically significant differences in 2-year results: HR
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26 for failure-free survival was 0.74 (0.49-1.10), $P = .13$. However, it must be cautioned that the
27
28 follow-up was too short for definitive confirmation. Data from the second patient-data based
29
30 meta-analysis by MAC-NPC Collaborative Group²¹ showed that both groups achieved
31
32 significant benefit in OS: the concurrent-adjuvant group showed robust long-term results (HR
33
34 = 0.65 [0.56-0.76], with 5/6 comparisons individually significant); the corresponding results
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36 in the concurrent alone group was HR = 0.80 [0.70-0.93] (2/7 comparisons individually
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38 significant, the greatest benefit was observed in a trial aimed for Stage II).
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40 Concurrent-adjuvant chemotherapy remains a recommendation with Level 1A evidence; the
41
42 use of this sequence as the standard arm in the current trial is relevant.
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53 All the reported trials on Concurrent-adjuvant chemotherapy used concurrent cisplatin
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55 and adjuvant PF; hence PF is used as the standard non-concurrent chemotherapy in the
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4 current trial. Unlike other head and neck cancers, no trial has yet been conducted on
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6 non-keratinizing NPC to evaluate the benefit of adding taxane or compare the efficacy of
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8 taxane versus fluorouracil. As our previous exploratory study on NPC-9901 and NPC-9902
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10 Trials⁶ showed dose-dependent effect of fluorouracil on distant failure, we focus on exploring
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12 for better uracil agent.
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17 As explained in the Introduction, the current trial is designed to evaluate three
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19 potential strategies: induction-concurrent sequence, use of capecitabine, and accelerated
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21 fractionation. In concurrence with a review¹⁸ of reported studies, patients treated with
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23 induction-concurrent regimens had excellent tolerance in the non-concurrent phase, but
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25 decreased tolerance in the concurrent phase. Acceleration further affected the proportion of
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27 patients with 3 concurrent cycles. Such interacting variations (Table 2) may affect the
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29 ultimate efficacy of the induction and the acceleration strategies.
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35 Regarding the change to induction-concurrent sequence, there are five randomized
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37 studies by other groups, all used concurrent alone chemotherapy as the standard arm. Despite
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39 the encouraging results of single-arm studies, three reported randomized studies showed
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41 conflicting results. Hui et al.²² (adding induction cisplatin and docetaxel, n = 65) showed
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43 significantly better 3-year OS, but both Fountzilas et al.²³ (adding cisplatin, epirubicin and
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45 paclitaxel, n = 141) and Tan et al.²⁴ (adding carboplatin, gemcitabine and paclitaxel, n = 172)
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47 did not achieve OS benefit. Two trials are still on-going.
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53 Preliminary results from the current trial (Tables 3 and 4, Fig. 2) showed that
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55 changing the sequence per se, as shown by comparison of Induction-PF versus Adjuvant-PF,
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4 did not achieve statistically significant improvement in efficacy. More encouraging results
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6 were achieved by changing both the sequence and the induction regimen: unadjusted
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8 comparison of induction-PX versus Adjuvant-PF showed favorable trend in PFS when given
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10 with Conventional-fractionated RT ($P = .045$). Multivariate analyses further showed that
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12 when adjusted for other significant factors and fractionation, PX group had significantly
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14 lower hazard in progression ($P = .002$) and death ($P = .001$). When the two induction groups
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16 were combined for evaluation of sequence Induction versus Adjuvant, unadjusted
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18 comparisons did not reach statistical significance, but adjusted analyses also showed lower
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20 hazard in progression ($P = .016$) and death ($P = .006$).
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28 The change from fluorouracil to capecitabine has been extensively studied in other
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30 solid cancers. Studies comparing capecitabine versus fluorouracil in gastrointestinal cancers
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32 consistently confirmed that capecitabine is a favorable alternative with at least equivalent
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34 efficacy, lower toxicities and better patient acceptance.¹⁰⁻¹⁴ However the conclusion on
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36 survival benefit is less definitive. Two large trials on metastatic colorectal cancer^{12,13} showed
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38 superior response rates, but only equivalent PFS and OS. The X-ACT Trial on adjuvant
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40 therapy for colon cancer¹⁴ showed significant survival benefit on preplanned multivariate
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42 analyses, but only borderline benefit on unadjusted comparisons. A meta-analysis comparing
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44 capecitabine- versus fluorouracil-containing chemotherapy for colorectal and gastric
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46 cancers¹⁵ showed that unadjusted HR for OS was 0.94 ($P = .049$).
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54 Promising efficacy of capecitabine has been reported in a phase II study²⁵ on patients
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56 with recurrent and metastatic NPC: 24% showed overall response with significant tumor
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4 regression after 3 cycles despite heavy pretreatment with cisplatin-based chemotherapy. The
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6 current trial is the first randomized trial to evaluate this uracil agent for NPC. Replacing
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8 fluorouracil (given by intravenous infusion) by capecitabine (given orally) is obviously more
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10 convenient and welcomed by patients. In addition, this regimen incurred less neutropenia and
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12 electrolyte disturbance (Table 5). In terms of efficacy, unadjusted comparison of
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14 Induction-PX versus Induction-PF did not show significant difference, but adjusted analysis
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16 showed that Induction-PX had lower hazard in death ($P = .038$).
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22 Regarding the change to accelerated fractionation, a meta-analysis²⁶ showed that
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24 altered fractionation, particularly hyper-fractionation, can improve survival. However, both
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26 the GORTEC 99-02 trial²⁷ and the RTOG-0129 Study²⁸ showed that acceleration is not
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28 beneficial for patients with concurrent chemoradiotherapy. It should be noted that all these
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30 studies only focused on other head and neck cancers. The only trial that specifically focused
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32 on NPC is the NPC-9902 Trial,⁷ which in contrast suggested that acceleration combined with
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34 concurrent-adjuvant chemoradiotherapy could further improve the failure-free rate for
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36 T3-4N0-1 disease. However, it must be cautioned that this finding can only be taken as
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38 hypothesis-generating as the trial was terminated early due to slow accrual, the sample size
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40 (189 patients) is smaller than the planned target, possibility of subtle biases and chance
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42 findings cannot be totally excluded.
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51 The current trial is the only trial that attempted to confirm this potential strategy. With
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53 shorter overall RT time, the proportion of patients with 3 concurrent cycles was inevitably
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55 low in the Accelerated group. With further lowering of tolerance by induction chemotherapy,
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4 even the proportion with ≥ 2 concurrent cycles was affected. In concurrence with trials^{27,28} on
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7 other head and neck cancers, the current finding showed that acceleration did not improve
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9 efficacy (Tables 3 and 4, Fig. 3). In addition, acceleration incurred significantly higher
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11 incidence of acute mucositis and dehydration (Table 5). Together with the logistic difficulty
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13 for arranging six fractions per week, acceleration is not recommended for patients treated
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15 with chemoradiotherapy, particularly those with induction-concurrent regimens.
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19 The current NPC-0501 Trial is a trial with largest sample size for NPC (802 evaluable
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21 patients), however, the trial is possibly still under-powered. A major weakness is that the trial
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23 design is too complex with inclusion of multiple arms and strata. This is further complicated
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25 by the change in protocol after the first interim analysis allowing centers with logistical
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27 difficulty to opt out of the Accelerated arms. To be pertinent, all comparisons on efficacy
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29 related to fractionation were based only on the 706 patients randomly assigned to all six arms.
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31 Another point that may further lead to difficulty in proving statistical difference is that 90%
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33 of patients in the current trial were irradiated with modern intensity-modulated technique; the
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35 magnitude of benefit contributed by chemotherapy is likely to be lower than past series
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37 irradiated with less optimal techniques. Lastly, the median follow-up for this preliminary
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39 analysis is 3.3 years; longer observation is needed to confirm the long-term therapeutic ratio.
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49 Nonetheless, the current findings provide valuable data for guiding clinical practice and
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51 future trials.
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54 In conclusion, our preliminary results showed that the benefit of changing to
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56 induction-concurrent sequence remains uncertain; the Induction-PF regimen did not achieve
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4 statistical significant improvement in efficacy. Changing both the sequence and regimen to
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6 Induction-PX achieved more favorable trends in efficacy. In view of convenience, favorable
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8 toxicity profile and at least comparable efficacy, replacing fluorouracil with capecitabine
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10 warrants further validation. Accelerated fractionation is not recommended for NPC patients
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14 treated by chemoradiotherapy.
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TABLE 1. Basic Characteristics and Radiotherapy of the Whole Series (n = 802)

	Arm 1A (n=160)	Arm 2A (n=161)	Arm 3A (n = 165)	Arm 1B (n=104)	Arm 2B (n = 110)	Arm 3B (n = 102)
Fractionation	Conventional	Conventional	Conventional	Accelerated	Accelerated	Accelerated
Regimen	Adjuvant-PF	Induction-PF	Induction-PX	Adjuvant-PF	Induction-PF	Induction-PX
<u>Patient</u>						
Age: mean (SD) years	48 (9)	48 (9)	48 (9)	49 (8)	48 (10)	49 (9)
Sex - Male	117 (73%)	116 (72%)	133 (81%)	85 (82%)	84 (76%)	78 (76%)
Performance status						
0	116 (73%)	106 (66%)	112 (68%)	70 (67%)	67 (61%)	65 (64%)
1	43 (27%)	54 (34%)	53 (32%)	33 (32%)	42 (38%)	36 (35%)
2	1 (0.6%)	1 (0.6%)	0 (0%)	1 (1.0%)	1 (0.9%)	1 (1.0%)
<u>Tumor factor</u>						
Staging method						
MRI ± CT	155 (97%)	156 (97%)	158 (96%)	100 (96%)	104 (95%)	102 (100%)
CT alone	5 (3%)	5 (3%)	7 (4%)	4 (4%)	6 (5%)	0 (0%)
T-classification						
T1-2	24 (15%)	33 (20%)	35 (21%)	28 (27%)	26 (24%)	21 (21%)
T3	113 (71%)	105 (65%)	103 (62%)	60 (58%)	66 (60%)	61 (60%)
T4	23 (14%)	23 (14%)	27 (16%)	16 (15%)	18 (16%)	20 (20%)
N-classification						
N0-1	58 (36%)	46 (29%)	37 (22%)	25 (24%)	25 (23%)	25 (25%)
N2	77 (48%)	92 (57%)	104 (63%)	61 (59%)	67 (61%)	58 (57%)
N3	25 (16%)	23 (14%)	24 (15%)	18 (17%)	18 (16%)	19 (19%)
Stage-group						
III	114 (71%)	118 (73%)	117 (71%)	74 (71%)	76 (69%)	67 (66%)

TABLE 1. Continued.

Stage-group						
IVA - IVB	46 (29%)	43 (27%)	48 (29%)	30 (29%)	34 (31%)	35 (34%)
LDH: mean (SD) iu/L	226 (79)	237 (115)	236 (93)	236 (94)	244 (91)	252 (126)
<u>Radiotherapy</u>						
Technique						
2DRT	3 (2%)	5 (3%)	5 (3%)	7 (7%)	2 (2%)	2 (2%)
3DRT	6 (4%)	2 (1%)	2 (1%)	3 (3%)	0 (0%)	4 (4%)
IMRT	148 (93%)	152 (94%)	154 (93%)	94 (90%)	104 (95%)	94 (92%)
Total Dose: mean (SD) Gy	69.7 (2.2)	69.6 (3.2)	69.9 (1.7)	69.6 (1.7)	69.3 (5.8)	69.6 (1.9)
Overall time: mean (SD) day	47 (2.7)	47 (3.0)	47 (2.8)	42 (3.3)	41 (4.4)	41 (3.1)

Abbreviations: SD, standard deviation; P, cisplatin; F, fluorouracil; X, capecitabine; MRI, magnetic resonance imaging; CT, computed tomography; LDH, lactate dehydrogenase; 2DRT, 2-dimensional; 3DRT, 3-dimensional conformal; IMRT, intensity-modulated radiotherapy technique.

TABLE 2. Tolerance to Chemotherapy

Chemotherapy	<u>Conventional Fractionation</u>			<u>Accelerated Fractionation</u>		
	Adjuvant-PF (Arm 1A)	Induction-PF (Arm 2A)	Induction-PX (Arm 3A)	Adjuvant-PF (Arm 1B)	Induction-PF (Arm 2B)	Induction-PX (Arm 3B)
<u>Concurrent</u>						
None	3%	7%	5%	0	3%	5%
1 cycle	3%	3%	4%	3%	6%	7%
2 cycles	40%	49%	58%	75%	85%	83%
3 cycles	55%	40%	33%	22%	6%	5%
<u>Non-Concurrent</u>						
None	19%	1%	1%	17%	1%	0%
1 cycle	8%	6%	7%	12%	8%	3%
2 cycles	8%	4%	7%	8%	0	9%
3 cycles	65%	89%	85%	63%	91%	88%

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

TABLE 3. Efficacy – Tumor Control Rates and Stratified Comparisons

Factor	Strata	Progression-Free Survival	Overall Survival
<u>Actuarial Rate at 3-year</u>			
Arm 1A		75%	83%
Arm 2A		79%	85%
Arm 3A		81%	91%
Arm 1B		79%	87%
Arm 2B		77%	90%
Arm 3B		76%	88%
Arm 2-3A		80%	88%
Arm 2-3B		76%	89%
<u>P Value on Comparison by Stratified Log Rank Test</u>			
Regimen group			
Induction-PF vs Adjuvant PF	Conventional (Arm 2A vs 1A)	.30	.30
	Accelerated (Arm 2B vs 1B)	.75	.73
	Overall	.33	.33
Induction-PX vs Adjuvant PF	Conventional (Arm 3A vs 1A)	.045	.12
	Accelerated (Arm 3B vs 1B)	.66	.24
	Overall (Arms 3A-B vs 1A-B)	.079	.055
Induction-PX vs Induction-PF	Conventional (Arm 3A vs 2A)	.34	.61
	Accelerated (Arm 3B vs 2B)	.90	.34
	Overall	.44	.30
Sequence			
Induction vs Adjuvant	Conventional (Arms 2-3A vs 1A)	.073	.12
	Accelerated (Arms 2-3B vs 1B)	.66	.39
	Overall	.11	.089
Fractionation			
Accelerated vs Conventional	Adjuvant-PF (Arm 1B vs 1A)	.68	.96
	Induction-PF (Arm 2B vs 2A)	.84	.44
	Induction-PX (Arm 3B vs 3A)	.31	.81
	Overall	.68	.55

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

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TABLE 4. Multivariate Analyses on Independent Significance of Experimental Intervention on Tumor Control: Hazard Ratio (95% Confidence Interval) and *P* Value

	Progression-Free Survival	Overall Survival
<u>Part I: Regimen Groups and Fractionation in Patients Randomized to All Six Arms (n = 706)</u>		
Regimen Groups	.009	.003
Induction-PF vs Adjuvant-PF	0.82 (0.57-1.19)	0.76 (0.48-1.19)
	.29	.23
Induction-PX vs Adjuvant-PF	0.54 (0.36-0.80)	0.42 (0.25-0.70)
	.002	.001
Fractionation: Acceleration vs Conventional	1.13 (0.82-1.54)	1.11 (0.75-1.62)
	.46	.61
<u>Part II: Chemotherapy Sequence and Fractionation in Patients Randomized to All Six Arms (n = 706)</u>		
Sequence: Induction vs Adjuvant	0.67 (0.48-0.93)	0.57 (0.39-0.86)
	.016	.006
Fractionation: Acceleration vs Conventional	1.14 (0.83-1.56)	1.12 (0.76-1.64)
	.41	.57
<u>Part III: Regimen and Fractionation in Patients Randomized to Induction Arms (n = 473)</u>		
Regimen: Induction-PX vs Induction -PF	0.67 (0.44-1.02)	0.57 (0.34-0.97)
	.059	.038
Fractionation: Acceleration vs Conventional	1.34 (0.90-2.01)	1.31 (0.80-2.18)
	.16	.30

The above analyses were adjusted for other significant covariates including stage, lactic dehydrogenase, radiotherapy technique, center, gender and age.

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine.

TABLE 5. Safety – Major Toxicity (Grade 3 or Above)

	<u>Regimen group</u>	<u>Sequence</u>	<u>Fractionation</u>
	Induction-PX vs Induction-PF	Induction	Accelerated
	vs Adjuvant-PF	vs Adjuvant	vs Conventional
<u>Acute Toxicity (grade ≥3): cumulative rate %</u>			
<u>Concurrent phase</u>			
Mucositis (radiation-induced)	30% vs 33% vs 32%	31% vs 32%	38% ¹ vs 27%
Dermatitis (radiation-induced)	3% vs 4% vs 3%	3% vs 3%	3% vs 4%
Dysphagia	8% vs 5% vs 6%	7% vs 6%	8% vs 6%
Dehydration	3% vs 3% vs 3%	3% vs 3%	4% ¹ vs 2%
Neutropenia	6% ¹ vs 4% ^{1,2} vs 8%	5% ¹ vs 8%	4% vs 8%
Anemia	8% vs 8% vs 1%	8% vs 1%	5% vs 6%
Thrombocytopenia	4% ¹ vs 2% vs 0%	3% ¹ vs 0%	2% vs 2%
Infection	3% vs 2% vs 4%	2% vs 4%	4% vs 3%
Vomiting	2% vs 2% vs 9%	2% vs 9%	4% vs 5%
Gastrointestinal	1% vs 0.4% vs 2%	0.7% vs 2%	2% vs 0.8%
Renal impairment	3% vs 3% ¹ vs 1%	3% ¹ vs 1%	3% vs 2%
Electrolyte disturbance	2% vs 2% ² vs 3%	2% vs 3%	3% vs 2%
Peripheral neuropathy	0.4% ¹ vs 0% ¹ vs 0%	0.2% ¹ vs 0%	0% vs 0.2%
Weight loss	2% vs 2% vs 2%	2% vs 2%	2% vs 2%
Others	0.4% vs 0.4% vs 1.1%	0.4% vs 1.1%	0.6% vs 0.6%
Any acute toxicity	26% ¹ vs 26% ¹ vs 45%	26% ¹ vs 45%	32% vs 32%
<u>Sequential phase</u>			
Mucositis (radiation-induced)	4% vs 4% vs 5%	4% vs 5%	7% ¹ vs 3%
Dermatitis (radiation-induced)	5% vs 3% vs 6%	4% vs 6%	7% vs 4%
Dysphagia	1% vs 2% vs 1%	2% vs 1%	2% vs 1%
Dehydration	3% vs 2% vs 1%	3% vs 1%	3% ¹ vs 1%
Neutropenia	28% ¹ vs 39% ^{1,2} vs 13%	33% ¹ vs 13%	31% vs 24%
Anemia	6% vs 5% vs 8%	5% vs 8%	7% vs 6%
Thrombocytopenia	5% ¹ vs 2% vs 2%	3% ¹ vs 2%	3% vs 3%
Infection	6% vs 3% vs 3%	5% vs 3%	6% vs 3%
Vomiting	10% vs 4% vs 1%	7% vs 1%	7% vs 4%
Gastrointestinal	5% vs 7% vs 4%	6% vs 4%	7% vs 5%
Renal impairment	3% vs 4% ¹ vs 1%	3% ¹ vs 1%	3% vs 2%
Electrolyte disturbance	4% vs 7% ² vs 3%	5% vs 3%	6% vs 4%
Peripheral neuropathy	10% ¹ vs 6% ¹ vs 2%	8% ¹ vs 2%	7% vs 6%
Weight loss	1% vs 2% vs 8%	1% vs 8%	3% vs 4%
Others	5% vs 3% vs 1%	4% vs 1%	2% vs 3%
Any acute toxicity	48% ¹ vs 52% ¹ vs 19%	50% ¹ vs 19%	44% vs 37%
<u>Late Toxicity (grade ≥3): actuarial rate at 3-year</u>			
Central nervous system	0.9% vs 0.8% vs 0.8%	0.9% vs 0.8%	1.0% vs 0.7%

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Ear toxicity	8% vs 6% vs 8%	7% vs 8%	6% vs 10%
Soft tissue/bone damage necrosis	1.2% vs 0.4% vs 1.7%	0.8% vs 1.7%	0.4% vs 1.6%
Others	1.5% vs 0.4% vs 2.0%	0.9% vs 2.0%	2.1% vs 0.6%
Any late toxicity	10% vs 7% vs 12%	9% vs 12%	8% vs 12%

Abbreviations: P, cisplatin; F, fluorouracil; X, capecitabine;

Peripheral neuropathy (sensory and/or motor) irrespective of persistence;

Ear toxicity (hearing impairment and/or otitis) irrespective of time of onset;

Central nervous system (temporal lobe necrosis, brainstem damage and/or cranial neuropathy);

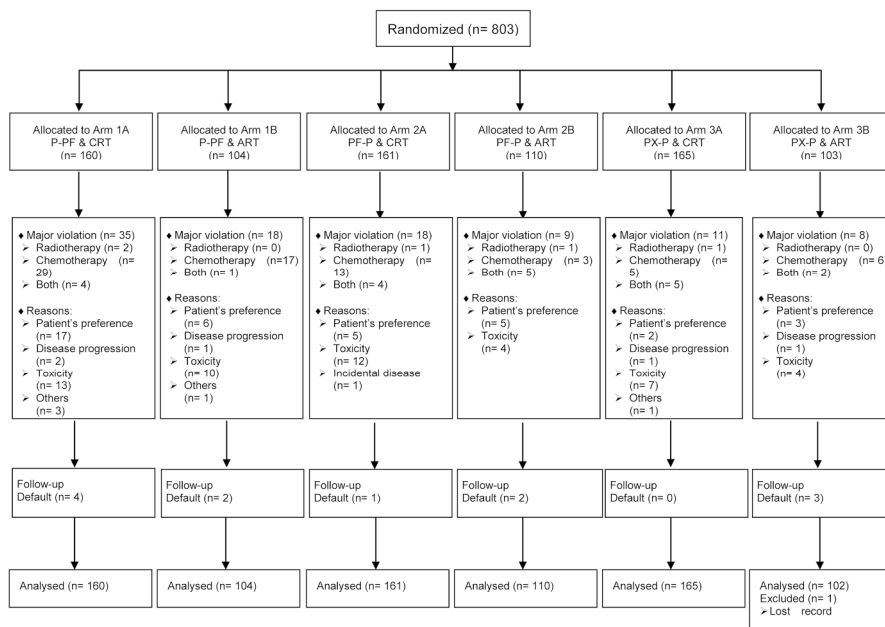
Significantly higher toxicity ($P < .05$): ¹Experimental vs standard group, ²Induction-PF vs Induction-PX

FIGURE LEGENDS

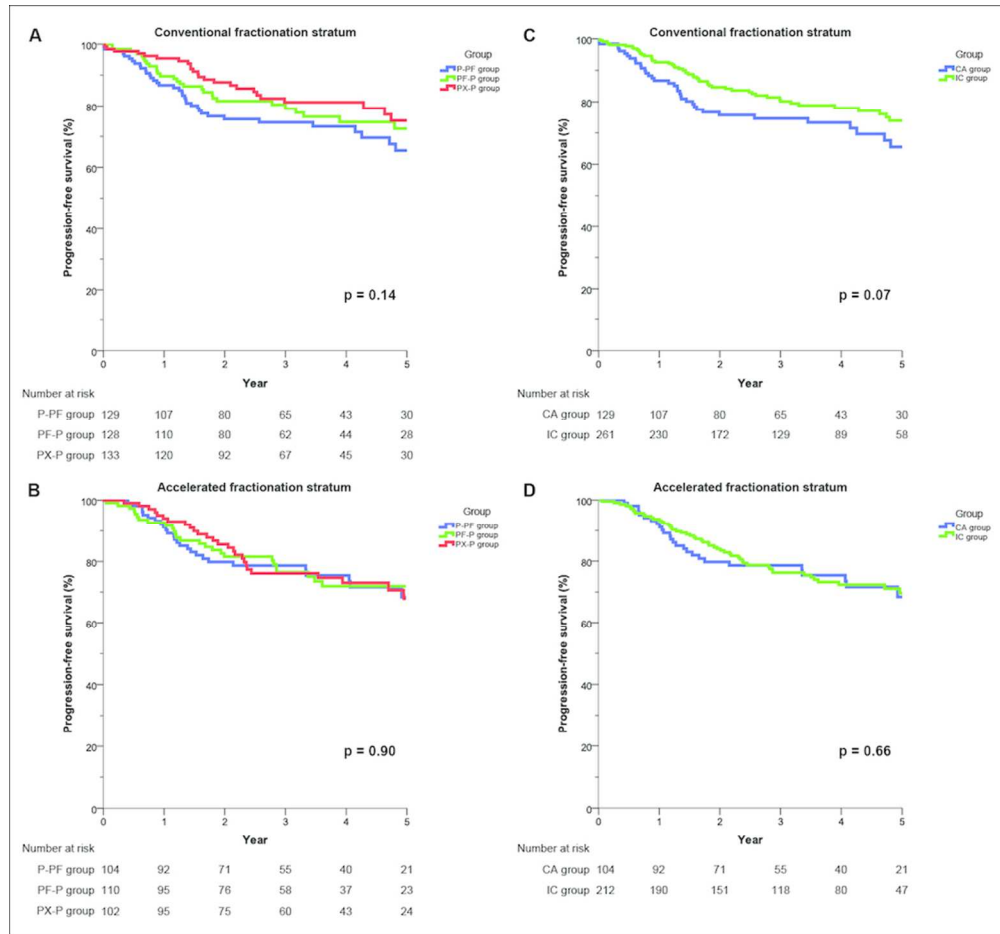
FIGURE 1. CONSORT diagram of the whole series in NPC-0501 Trial.

FIGURE 2. Comparison of progression-free survival by (A) regimen groups in patients with conventional-fractionation; (B) regimen groups in patients with accelerated -fractionation; (C) chemotherapy sequence in patients with conventional-fractionation; and (D) chemotherapy sequence in patients with accelerated -fractionation.

FIGURE 3. Comparison of progression-free survival by fractionation (A) adjuvant cisplatin-fluorouracil group; (B) induction cisplatin-fluorouracil group; and (C) induction cisplatin-capecitabine group.

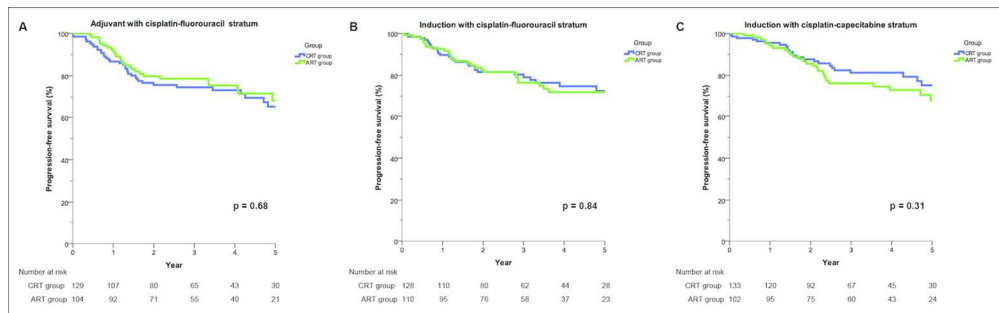


CONSORT diagram of the whole series in NPC-0501 Trial.
211x147mm (300 x 300 DPI)



Comparison of progression-free survival by (A) regimen groups in patients with conventional-fractionation; (B) regimen groups in patients with accelerated -fractionation; (C) chemotherapy sequence in patients with conventional-fractionation; and (D) chemotherapy sequence in patients with accelerated -fractionation. 254x236mm (100 x 100 DPI)

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Comparison of progression-free survival by fractionation (A) adjuvant cisplatin-fluorouracil group; (B) induction cisplatin-fluorouracil group; and (C) induction cisplatin-capecitabine group. 380x118mm (100 x 100 DPI)

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