Supplementary Materials

Supplementary Patients and Method

Inclusion criteria and exclusion criteria

The following inclusion criteria were used: (1) patients with biopsy-proven WHO type II or III; (2) age ≥18 years; ECOG of 0 to 2; and (3) adequate hematologic, renal, and hepatic function.

The following exclusion criteria were used: (1) previously received any anticancer therapy; (2) were younger than 18 years old; (3) were pregnant or lactating; (4) had a history of previous or synchronous malignant tumours; or (5) were NPC patients with primary metastasis; (6) lost to follow-up.

The methodology of the 2DRT, 3DRT and IMRT

The 2DRT technique consists of 3 phases [1]. In phase I, the lateral-opposed facial-cervical fields were used for the primary tumour and enlarged neck nodes while a lower anterior cervical field was applied to the lower cervical lymphatics. Phase II was applied after treatment with 40 Gy, aiming to avoid the spinal cord. In this phase, 3 fields (lateral-opposed plus anterior facial fields) were used for the nasopharyngeal region and an anterior cervical field for the whole neck. Phase III was used after a dose from 50 to 60 Gy (based on the T-stage), to protect the brainstem, optic chiasma, and temporal lobes from radiation. A postero-lateral field was applied in the supplementary treatment for patients with bulky parapharyngeal extension. An accumulated

radiation dose from 68 to 76 Gy was administered to the primary tumour, with 2 Gy per fraction. Then, 60 to 64 Gy was applied to the involved areas and 50 Gy to the uninvolved areas. All of the patients received treatment 5 days per week, with one fraction each day, and a variation of 5% over or below the target was accepted.

The details of the 3DRT technique were reported previously [2]. The gross tumour volume (GTV) was outlined according to the tumour extent represented by the imaging and endoscopic information. A radiation dose of 70 Gy for the clinical target volume (CTV1) covered the entire nasopharynx and the GTV with a margin of 2-5 mm. The CTV2 with a dose of 60 Gy involved high-risk local structures (including the parapharyngeal spaces, the posterior third of the nasal cavities and maxillary sinuses, pterygoid processes, base of skull, lower half of sphenoid sinus, anterior half of the clivus, and petrous tips), bilateral retropharyngeal nodes, and upper lymphatic (Levels II, III, and VA). For the CTV3 aiming at 50 Gy, the area included the remaining potential sites of local infiltration up to the roof of the sphenoid sinus and bilateral lower lymphatics (Levels IV and VB). Anterior-posterior opposed fields were applied to the cervical region with a 2-3 cm shield to limit the radiation to the larynx and oesophagus.

The IMRT technique consists of 9 coplanar beams to cover the entire region [3]. To describe the clinical target volume, the same principle as 3DRT was applied. The margins of the planning tumour volume (PTV) for both GTV and

CTV usually ranged from 3 to 5 mm. The radiation dose per protocol was defined as follows: a total of 68 Gy was applied in 30 fractions to PTV of the GTV of the primary tumour (GTV-P), and the treatment lasted for 6 weeks. Then, 60 to 64 Gy was administered to the PTV of the GTV of the regional lymph nodes (GTV-N) while 60 Gy was administered to the PTV of CTV-1 and 54 Gy to the PTV of CTV-2 and CTV-N. During the treatment, a dynamic, multileaf, intensity-modulating collimator was used to achieve the varied doses applied to the GTV, CTV and PTV. An anterior cervical field was also used for the lower neck. All of the patients received treatment 5 days per week, with one fraction each day.

When possible, salvage treatments were given to patients after documented relapse or when the disease was persistent. Salvage treatments included reirradiation, chemotherapy, and surgery.

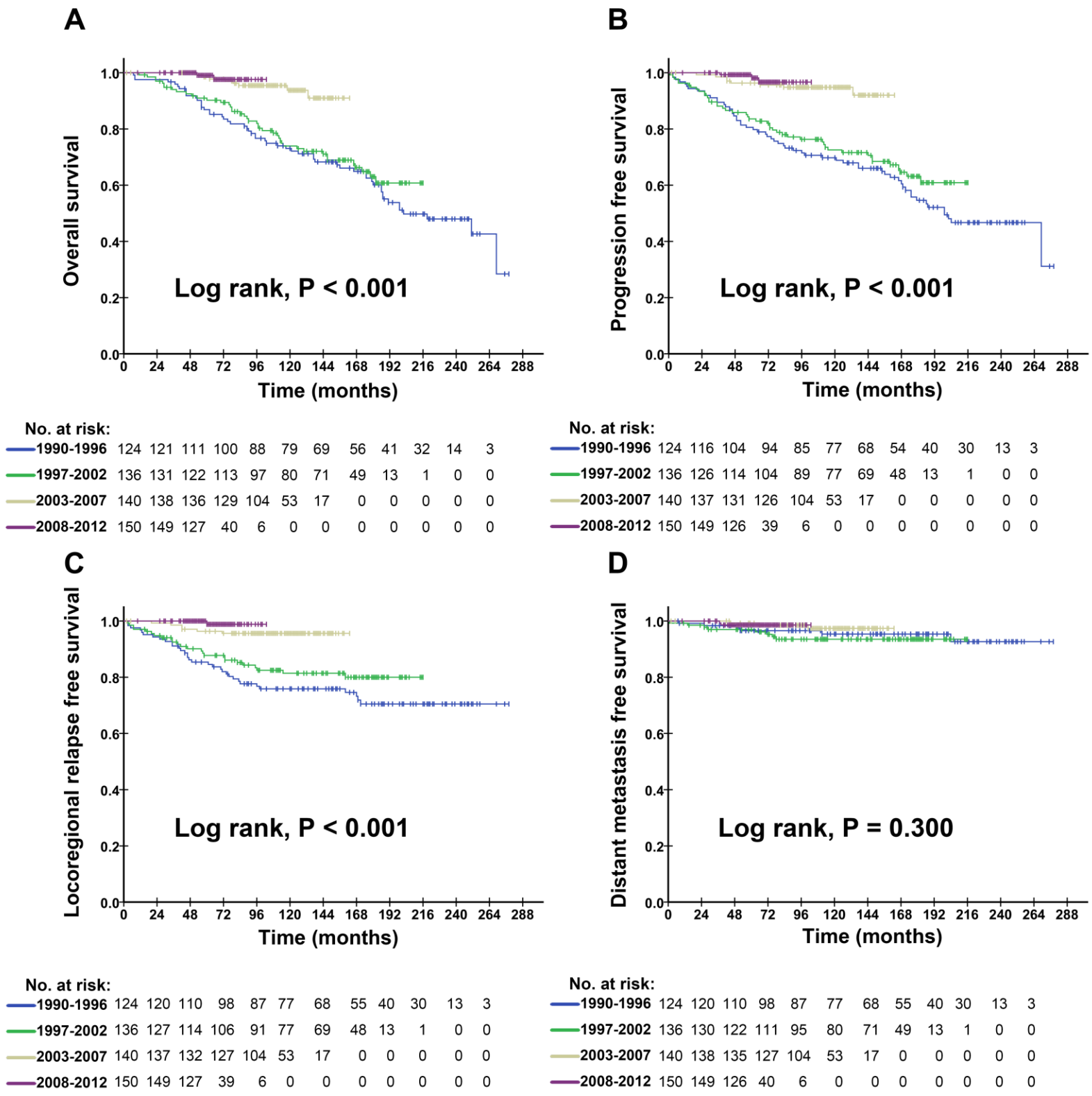
References

1. Ma J, Mai HQ, Hong MH et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2001; 19: 1350-1357.

2. Lee AW, Ng WT, Hung WM et al. Major late toxicities after conformal radiotherapy for nasopharyngeal carcinoma-patient- and treatment-related risk factors. Int J Radiat Oncol Biol Phys 2009; 73: 1121-1128.

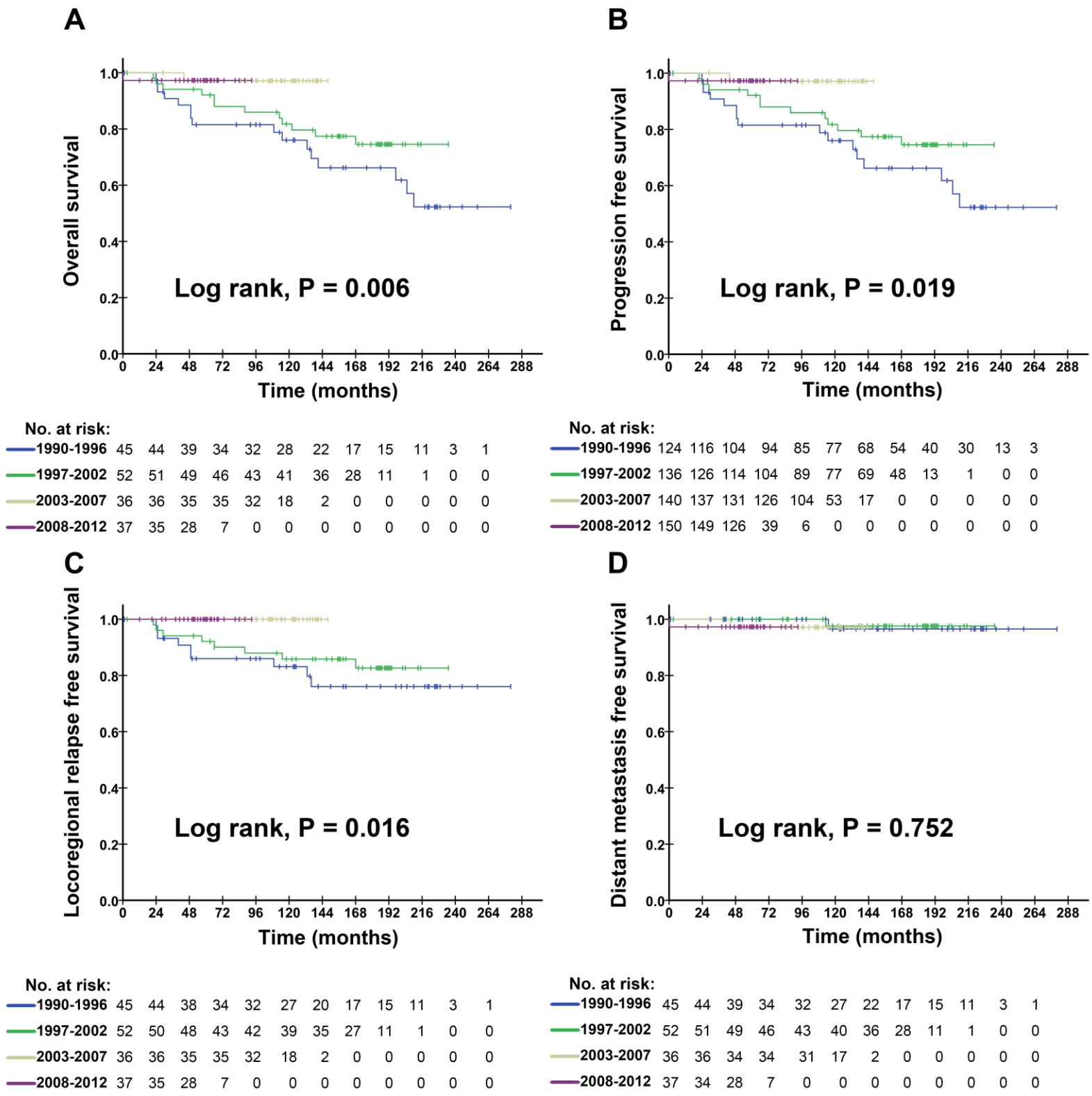
3. Lai SZ, Li WF, Chen L et al. How does intensity-modulated radiotherapy

versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? International Journal of Radiation Oncology Biology Physics 2011; 80: 661-668.



eFigure1. Kaplan-Meier survival curves for the male patient among four calendar periods in the study population.

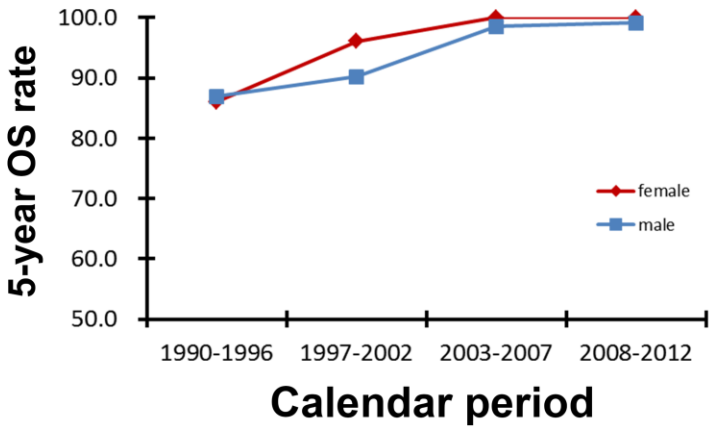
Overall survival (A), progression free survival (B), locoregional relapse free survival (C) and distant metastasis free survival (D) compared in the entire cohort of stage I NPC patients. *P* values were calculated using the unadjusted log-rank test.



eFigure2. Kaplan-Meier survival curves for the female patient among four calendar periods in the study population.

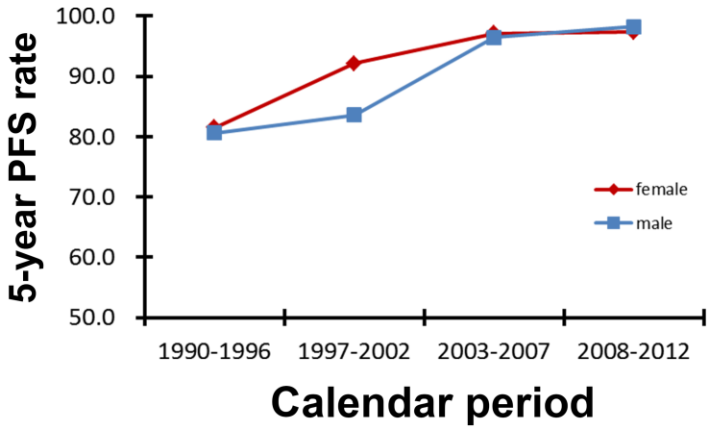
Overall survival (A), progression free survival (B), locoregional relapse free survival (C) and distant metastasis free survival (D) compared in the entire cohort of stage I NPC patients. *P* values were calculated using the unadjusted log-rank test.

A



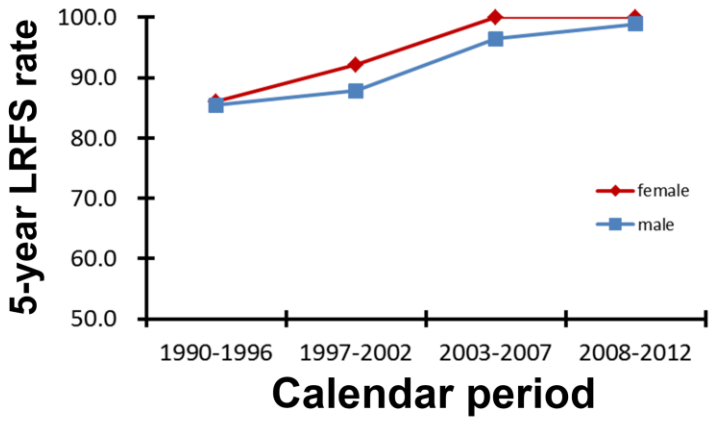
Gender	5-year overall survival rate (95% CI), %			
	1990-1996	1997-2002	2003-2007	2008-2012
Female	86.0 (75.6-96.4)	96.1 (90.8-100.0)	100.0(100.0-100.0)	100.0 (100.0-100.0)
Male	86.9 (80.8-93.0)	90.2 (85.1-95.3)	98.5 (96.5-100.0)	99.1 (97.3-100.0)

B



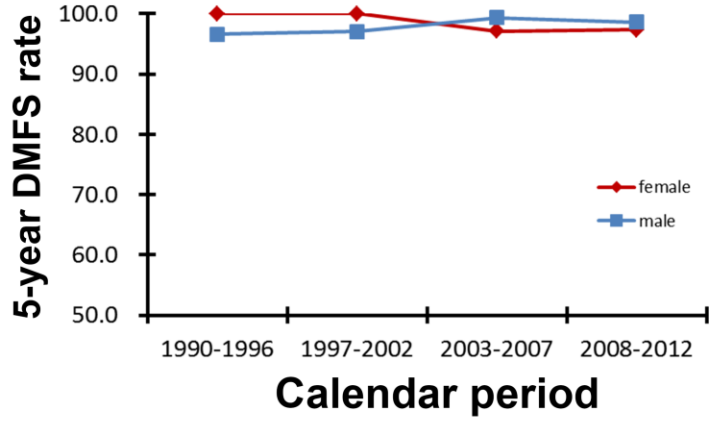
Gender	5-year progression free survival rate (95% CI), %			
	1990-1996	1997-2002	2003-2007	2008-2012
Female	81.5 (69.9-93.1)	92.1 (84.7-99.5)	97.1 (91.6-100.0)	97.3 (92.0-100.0)
Male	80.6 (73.5-87.7)	83.6 (77.3-89.9)	96.4 (90.9-100.0)	98.2 (95.7-100.0)

C



Gender	5-year locoregional relapse free survival rate (95% CI), %			
	1990-1996	1997-2002	2003-2007	2008-2012
Female	86.0 (75.6-96.4)	92.1 (84.7-99.5)	100.0(100.0-100.0)	100.0(100.0-100.0)
Male	85.4 (79.1-91.7)	87.8 (82.1-93.5)	96.4 (93.3-99.5)	98.9 (96.7-100.0)

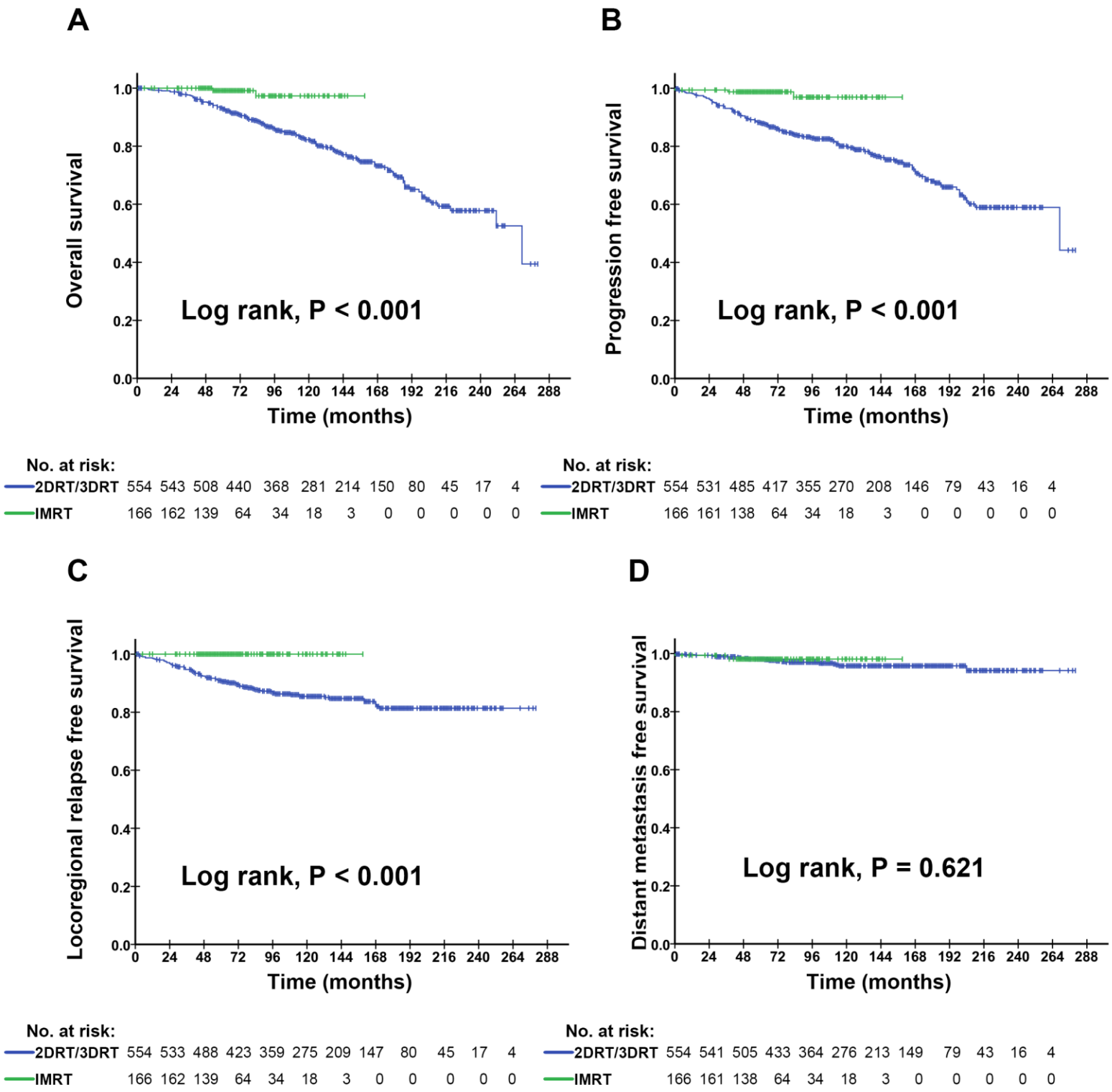
D



Gender	5-year distant metastasis free survival rate (95% CI), %			
	1990-1996	1997-2002	2003-2007	2008-2012
Female	81.5 (69.9-93.1)	92.1 (84.7-99.5)	97.1 (91.6-100.0)	97.3 (92.0-100.0)
Male	80.6 (73.5-87.7)	83.6 (77.3-89.9)	96.4 (90.9-100.0)	98.2 (95.7-100.0)

eFigure3. The trends of 5-year survival rates for two genders subgroups in the four calendar periods.

The 5-year overall survival rate (A), progression free survival rate (B), locoregional relapse free survival rate (C) and distant metastasis free survival rate (D) were shown in different age subgroups in 1990-1996, 1997-2002, 2003-2007, and 2008-2012



eFigure4. Kaplan-Meier survival curves for the 2DRT/3DRT arm and IMRT arm in the patients diagnosed from 1990 to 2012.

Overall survival (A), progression free survival (B), locoregional relapse free survival (C) and distant metastasis free survival (D) compared in the stage I NPC patients diagnosed in 2003 and later. *P* values were calculated using the unadjusted log-rank test.