Surrogate Endpoints for Overall Survival in locally advanced Nasopharynx carcinoma: Addendum to MAC-NPC update protocol

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The following protocol is an addendum to the full MAC-NPC protocol (available online: http://www.gustaveroussy.fr/sites/default/files/meta-a-march2-protocol-mars-2010-f.pdf). Performing a surrogate endpoint evaluation was planned as one of the initial objectives of the meta-analysis, and discussed with the MAC-NPC steering committee, secretariat and investigators from the very beginning and during the investigators meeting on November 9, 2013.

Objectives

We have previously shown that progression-free survival (PFS) is an acceptable surrogate endpoint for overall survival (OS) in radiotherapy and chemotherapy trials in in squamous cell head and neck carcinoma[1]. Our primary objective is to study whether PFS is also a surrogate endpoint for the evaluation of chemotherapy in nasopharynx carcinoma clinical trials. Our secondary objective is to study whether the distant metastasis free survival (DMFS) is a surrogate endpoint of the OS for the evaluation of chemotherapy in nasopharynx carcinoma clinical trials. The assessment will make use of individual patient data from the MAC-NPC2 meta-analysis of the effect of chemotherapy.

Description of Included Trials

The present project will use individual patient data from the updated MAC-NPC meta-analysis, (19 trials included in the MAC-NPC2 meta-analysis[2,3]) plus one trial[4]. In that meta-analysis, a total number of 4,806 patients were analyzed. Patients were recruited between 1988 and 2010 and the overall median follow-up time was 7.7 years. Appendix 1, from Blanchard et al. (2015)[3], describes in details the trials. Differently from the initial publication of the meta-analysis, the trial by Xu et al (2012)[4] will be included although it compared two different CT timings. For that trial the reference arm will be the one with concomitant chemotherapy and the experimental arm the one with neoadjuvant chemotherapy.

Endpoint Definition

Overall survival (OS is defined as the time from randomization until death from any cause.

Progression-free survival (PFS) is defined as the time from randomization to first progression (loco-regional or distant) or death from any cause.

Distant metastasis free survival (DMFS) is defined as the time from randomization to the occurrence of a distant relapse or death from any cause. Because in some trials only the first event is recorded, patients with a local event as first event will be censored for DMFS. If both a local relapse and a distant failure were recorded at the same time, patients will be considered as having an event for DMFS. Patients who were alive and free from events at the end of the study will be censored at their date of last follow-up.

Statistical Methods

All trials compared RT alone with RT plus CT, or compared a treatment strategy (RT plus concomitant CT or RT plus induction CT or RT plus adjuvant CT) with the same treatment strategy plus CT (other timing). Both published and unpublished trials meeting the criteria will be included. All randomized patients will be analyzed in their allocated arm according to the intention-to-treat principle.

A correlation approach will be used to assess the validity of each endpoint as surrogate for overall survival (OS)[5]. This approach has already been used by Buyse et al.[6] to assess the relationship between PFS and overall survival in OS colorectal patients, by Sargent et al. [7] to investigate the relationship between disease-free survival and OS in the adjuvant setting of colon cancer, by Burzykowski et al.[8] in breast cancer, by Michiels et al.[1] in locally advanced head and neck cancer, and by Mauguen et al.[9] in lung cancer. This approach investigates correlation at a trial level and at an individual level.

Individual Level Surrogacy

The association between distributions of OS and the candidate surrogate endpoint will be evaluated by a bivariate survival model[10,11] (copula). Different copula models (Hougaard, Plackett) will be fitted[12] and the best one according to the Akaike's criterion will be chosen. An estimated spearman correlation coefficient ρ close to 1 will indicate a strong correlation between OS and the candidate surrogate.

Trial Level Surrogacy

Treatment effects will be estimated by log hazard ratios in bivariate survival models. The correlation between the treatment effects on the candidate surrogate and on OS will be quantified through a linear regression model, weighted by the trial size. If the estimated R will be close to 1, then the risk reduction for OS will be considered strongly correlated with the risk reduction for the candidate surrogate. As done by Mauguen et al.[9], the squared correlation R^2 will be considered as excellent if higher than 0.9, as very good if higher than 0.75, as good if higher than 0.5, as moderate if higher than 0.25, and as poor otherwise. Results will be compared to those obtained by the same regression model fitted on hazard ratios estimated in separate Cox models.

In order to enhance interpretation for the clinician's point of view, the correlation between effect of treatment on 2 year surrogate endpoint and 5-year OS will also be regarded. The event rates over time will be evaluated in order to explore whether other cut-off points are more appropriate.

Effective Surrogacy

The candidate surrogate endpoint will be acceptable only if its correlation coefficients ρ and R are close to 1.

Surrogate Threshold Effect

One objective of a surrogate endpoint is to predict the treatment effect on OS, based on the treatment effect on the surrogate endpoint. The Surrogate Threshold Effect (STE)[13] will be computed in order to estimate this prediction threshold: the STE is defined as the minimum treatment effect that is necessary on the surrogate to be able to predict a non-zero effect on overall survival. Its calculation is based on the linear regression used for the determination of trial level surrogacy.

Cross Validation

A leave-one-out cross-validation will be used to validate the results obtained[1]. For each trial, the model for the OS and the surrogate will be re fitted on the remaining 19 trials; the results of such refitted model will be used to predict the treatment effect on OS in the left-out trial, based on the effect of the treatment on the surrogate endpoint in the left-out trial. For each trial, the direct estimate of the hazard ratio will be compared to the predicted hazard ratio and 95% prediction interval.

Sensitivity analyses

A sensitivity analysis will be performed by calendar period: the 9 less recent trials (PWH-88, AOCOA, VUMCA-89, INT-0099, Japan-91, TCOG-94, PWHQEH-94, QMH-95, VUMCA-95) will be analyzed separately from the 11 most recent ones (SQNP01, NPC-9901, NPC-9902, Guangzhou 2001, NPC008, Guangzhou 2002-02, Guangzhou 2002-01, Guangzhou 2003, HeCOG, Shangai31, Guangzhou 2006).

The leave-one-out cross-validation procedure will be replicated with data censored at 2 years in the model for the surrogate of the left-out trial. This will allow evaluate whether early information on the surrogate predicts sufficiently well the long term effect on OS.

Publication Policy

Any publication arising from this project will be made *on behalf* of the MAC-NPC collaborative group and include a list of all investigators responsible for trials included in this study.

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Appendix 1 (from Blanchard et al, Lancet Oncology, 2015 plus one trial[4])

Trial (reference[&])	Inclusion period	Stage (TNM classification)	Histology, WHO classification	Radiotherapy, dose/duration	Chemotherapy		Patients randomized/ analysed	Median follow-up, years[**]
					Timing[§] (treatment arm)	Dose*Number of cycles		
PWH-88 [14]	1988–1991	II-IV (Ho)	3	T 66Gy/6·5weeks N- 58Gy, N+ 65·5Gy	Induction (E) and Adjuvant (E)	IC: Cisplatin 100mg/m² * 2 cycles Fluorouracil 1,000mg/m²/d_{2-4} * 2 cycles AC: Cisplatin 100mg/m² * 4 cycles Fluorouracil 1,000mg/m²/d * 4 cycles	82[†]/77	2.9
AOCOA [15]	1989–1993	II-IV (AJCC/UICC < 1997)	2–3	T 66–74Gy/6·5–7·.5weeks N- 60–66Gy, N+ 66–76Gy	Induction (E)	IC: Cisplatin 60mg/m² * 2–3 cycles Epirubicin 100mg/m² * 2–3 cycles	334/334	5.4
VUMCA-89 [16]	1989–1993	II-IV [#] (AJCC/UICC < 1997)	2–3	T 65–70Gy/6·5–7·5weeks N- 50Gy, N+ 65Gy	Induction (E)	IC: Bleomycin 15mg * 3 cycles Bleomycin 12mg/m²/d_{1-5} * 3 cycles Epirubicin 70mg/m² * 3 cycles Cisplatin 100mg/m² * 3 cycles	339/339	7.0
INT-0099 [17]	1989–1995	II-IV [ǂ] (AJCC/UICC < 1997)	1–3	T 70Gy/7weeks N- 50Gy, N+ 66–70Gy	Concomitant (E) and Adjuvant (E)	CC: Cisplatin 100mg/m² * 3 cycles AC: Cisplatin 80mg/m² * 3 cycles Fluorouracil 1,000mg/m²/d_{1-4} * 3 cycles	193[†]/193	16.8
Japan-91 [18]	1991–1998	I-IV (AJCC/UICC < 1997)	1–3	T 66–68Gy/6·5–7weeks N- 50Gy, N+ 66–68Gy	Induction (E)	IC: Cisplatin 80mg/m² * 2 cycles Fluorouracil 800mg/m²/d_{2-5} * 2 cycles	80/80	6.2
TCOG-94 [19]	1994–1999	III-IV (AJCC/UICC < 1997)	1–3	T 70–72Gy/7–8weeks N- 50Gy	Adjuvant (E)	AC: Cisplatin 20mg/m² * 9 cycles Fluorouracil 2,200mg/m² * 9 cycles Leucovorin 120mg/m² * 9 cycles	158[†]/158	15.0
PWHQEH-94 [20]	1994–1999	II-IV (AJCC/UICC 1997)	1–3	T 66Gy/6·5weeks N- 58Gy, N+ 65·5Gy	Concomitant (E)	CC: Cisplatin 40mg/m² weekly	350/350	14.1
QMH-95 [21]	1995–1997	II-IV (AJCC/UICC 1997)	1–3	T 62·5-68Gy/7weeks N 62·5–66Gy/7weeks (±boost 10Gy)	Concomitant (C, E) and Adjuvant (C, E)[*]	CC: UFT 600mg/d * 5–8 weeks AC: Cisplatin 100mg/m² * 6 cycles Fluorouracil1,000mg/m²/d_{1-3} * 6 cycles Vincristine 2mg * 6 cycles Bleomycin 30mg * 6 cycles Methotrexate 150mg/m² * 6 cycles	222[†]/222	14.0
VUMCA-95 (unpublished)	1995–2000	III-IV (AJCC/UICC < 1997)	1–3	T 70Gy/7weeks N- 50Gy, N+ 64–66Gy	Induction (C, E) and Concomitant (E)	IC: Bleomycin 10mg * 3 cycles Bleomycin 12mg/m²/d_{1-5} * 3 cycles Epirubicin 70mg/m² * 3 cycles Cisplatin 100mg/m² * 3 cycles CC: Hu 500–1,000mg/d * 7 cycles	509/509	5.8
SQNP01 [22]	1997–2003	II-IV [£] (AJCC/UICC 1997)	2–3	T 70Gy/7weeks	Concomitant(E) and Adjuvant (E)	CC: Cisplatin 25mg/m²/d_{1-4} * 3 cycles AC: Cisplatin 20mg/m²/d_{1-4} * 3 cycles Fluorouracil1,000mg/m²/d_{1-4} * 3 cycles	221/221	11.9
NPC-9901 [23]	1999–2004	III-IV (AJCC/UICC 1997)	2–3	T ≥ 66Gy/6·6weeks; N ≥ 50Gy	Concomitant (E) and Adjuvant (E)	CC: Cisplatin 100mg/m² * 3 cycles AC: Cisplatin 80mg/m² * 3 cycles Fluorouracil 1,000mg/m²/d_{1-4} * 3 cycles	348/348	10.4
NPC-9902 [24]	1999–2004	III-IV (AJCC/UICC 1997)	2–3	T ≥ 66Gy/5·5–6·6weeks[‡]	Concomitant (E) and Adjuvant (E)	CC: Cisplatin 100mg/m² * 3 cycles AC: Cisplatin 80mg/m² * 3 cycles Fluorouracil 1,000mg/m²/d_{1-4} * 3 cycles	189/189	10.6
Guangzhou 2001 [25]	2001–2003	III-IV (AJCC/UICC 1997)	2–3	T 70–74Gy/6–7·5weeks N- 50Gy, N+ 60–64Gy	Concomitant (E)	CC: Oxaliplatin 70mg/m² * 6 cycles	115/115	9.6
NPC008 [26]	2002–2004	III-IV (AJCC/UICC 1997)	2–3	T 66Gy/6·6weeks	Induction (E) and Concomitant (C, E)	IC: Docetaxel 75mg/m² * 2 cycles Cisplatin 75mg/m² * 2 cycles CC: Cisplatin 40mg/m² * 7 cycles	65/65	8.4

Trial (reference[&])	Inclusion period	Stage (TNM classification)	Histology, WHO classification	Radiotherapy, dose/duration	Chemotherapy		Patients randomized/ analysed	Median follow-up, years[**]
					Timing[§] (treatment arm)	Dose*Number of cycles		
Guangzhou 2002-02 [27]	2002–2005	III-IV (Chinese 1992)	1–3	T 66–78Gy/6·6–7·8weeks N+ 60–70Gy	Induction (C, E) and Concomitant (E)	IC: Floxuridine 750mg/m²/d * 2 cycles Carboplatin AUC=6 * 2 cycles CC:Carboplatin AUC=6 * 3 cycles	408[†]/408	7.4
Guangzhou 2002-01 [28]	2002–2005	III-IV (AJCC/UICC 1997)	2–3	T 68–70Gy/6·8–7weeks N- 50Gy, N+ 60–66Gy (±boost 10–14Gy)	Concomitant (E) and Adjuvant (E)	CC: Cisplatin 40mg/m² * 7 cycles AC: Cisplatin 80mg/m² * 3 cycles Fluorouracil 800mg/m²/d_{1-5} * 3 cycles	316/316	6.2
Guangzhou 2003 [29]	2003–2007	II-III (AJCC/UICC 2009)	2–3	T 68–70Gy/6.8–7weeks N- 50Gy, N+ 60–62Gy	Concomitant (E)	CC: Cisplatin 30mg/m² * 7 cycles	230/230	7.6
HeCOG [30]	2003–2008	II-IV (AJCC/UICC 2002)	1–3	T 66–70Gy/6·5–7weeks N- 50Gy, N+ 66–70Gy	Induction (E) and Concomitant (C, E)	IC: Epirubicin 75mg/m² * 3 cycles Paclitaxel 175mg/m² * 3 cycles Cisplatin 75mg/m² * 3 cycles CC: Cisplatin 40mg/m² * 7 cycles	144[†]/144	6.7
Shanghai[4,&]	2004–2007	III-IV (AJCC/UICC 2002)	2-3	T 70-76Gy/7weeks N- 50–60Gy, N+ 55–70Gy	Induction (E), Concomitant (C), and Adjuvant(C, E)	IC: Cisplatin 30mg/m²/d_{1-3} * 2 cycles Fluorouracil 500mg/m²/d_{1-3} * 2 cycles CC: Cisplatin 30mg/m²/d_{1-3} * 2 cycles Fluorouracil 500mg/m²/d_{1-3} * 2 cycles AC: Cisplatin 30mg/m²/d_{1-3} * 4 cycles Fluorouracil 500mg/m²/d_{1-3} * 4 cycles	338/338	5.6
Guangzhou 2006 [31]	2006–2010	II-IV [¶] (AJCC/UICC 2002)	2–3	T ≥66Gy/6–7weeks N- 50Gy, N+ 60–66Gy	Concomitant (C, E) and Adjuvant (E)	CC: Cisplatin 40mg/m² * 7 cycles AC: Cisplatin 80mg/m² * 3 cycles Fluorouracil 800mg/m²/d_{1-5} * 3 cycles	508/508	3.2

TNM = Tumour Nodes Metastasis; WHO = World Health Organization; PWH = Prince of Wales Hospital; AOCOA = Asian-Oceanian Clinical Oncology Association; VUMCA = International Nasopharynx Cancer Study Group (cavum); INT-0099 = SWOG (Southwest Oncology Group)-coordinated Intergroup trial, also known as SWOG 8892; TCOG = Taiwan Cooperative Oncology Group; PWHQEH = Prince of Wales Hospital, Queen Elizabeth Hospital; QMH = Queen Mary Hospital; SQNP = Singapore Naso-Pharynx; NPC: Nasopharyngeal Carcinoma; HeCOG = Hellenic Cooperative Oncology Group; AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer; T = Tumour; N- = negative neck lymph nodes; N+ = positive neck lymph nodes; E = Experimental arm; C = Control arm; IC = Induction Chemotherapy; AC = Adjuvant Chemotherapy; CC = Concomitant Chemotherapy; d = day; UFT = Uracil + Tegafur; Hu = hydroxyurea AUC = Area Under the Curve; RT = radiotherapy

[#] Inclusion criterion was stage III-IV but one patient had a stage II

[ǂ] Inclusion criterion was stage III-IV but five patients had a stage II

[£] Inclusion criterion was stage III-IV but one patient had a stage II

[¶] Inclusion criterion was stage III-IV except T3-4N0 of AJCC/UICC 2002 but one patient had a stage II with T2N1M0

[§] Timing(s) of chemotherapy randomized is (are) underlined. For the trials with two different CT timings (only one randomized), randomization was before the start of any treatment, except for TCOG-94 that randomized AC after RT starting on October 1997 and for QMH-95 in which the second randomization (for AC) was after RT

[*] 4 treatment arms: RT / RT + CC / RT + AC / RT + CC + AC. 4 comparisons: RT vs RT + CC / RT + AC vs RT + CC +AC / RT vs RT + AC / RT + CC vs RT + CC + AC

[‡] Conventional (CF) or accelerated fractionation (AF); 4 treatment arms: CF / CF + CC + AC/ AF / AF + CC + AC; 2 comparisons according to the type of radiotherapy

† Overall, 68 randomized patients had been excluded in the initial trial publications (PWH-88: 5; INT-0099: 46; QMH-95: 3; TCOG-94: 3; HeCOG: 3; Guangzhou 2002-02: 8) but 63 (1% of the patients of the meta-analysis) were recovered in the meta-analysis (only data for 5 patients from PWH-88 were not available)

[**] Follow-up was not significantly different between randomized arms for all trials

[&] References are those from Blanchard et al, Lancet Oncol, except for the Shanghai trial (Xu T, Zhu G, He X, Ying H, Hu C. A phase III randomized study comparing neoadjuvant chemotherapy with concurrent chemotherapy combined with radiotherapy for locoregionally advanced nasopharyngeal carcinoma: updated long-term survival outcomes. Oral Oncol. 2014 Feb;50(2):71-6.)

Appendix 2. Definition of progression in each trial

Trial	Definition of progression	Frequency of FU visits
PWH-88[14]	Complete response (CR) in cervical nodes was defined as complete disappearance of all palpable disease, and partial response (PR) as 50% or greater decrease in cross-sectional area (product of maximal measured diameters) of all neck nodes. Complete response in NP was defined as complete resolution of changes and negative biopsies of any suspicious changes. Partial response in NP was documented at nasopharyngoscopy as an overall impression of more than 50% regression.	
AOCOA[15]	Progressive disease was defined as the appearance of any new lesions or an increase of 25% or more in existent lesions.	
VUMCA-89[16]	Responses to chemotherapy assessed at the end of every cycle and before radiotherapy were defined under WHO response criteria	
INT-0099[17]	Standard SWOG criteria were used for response […] Responses were defined as follows: complete response--complete disappearance of measurable and palpable tumor confirmed by CT scan or MRI; partial response-tumor shrinkage >-50% of the sum of the product of the perpendicular diameters of all measurable lesions with no progression of assessable disease and no new lesions; stable/no change-disease parameters do not qualify as complete or partial response or progression; and progressive disease--growth of tumor by greater than 50% or an increase of 102 cm (whichever is smaller) of the sum of the product of the perpendicular diameters of all measurable lesions over the smallest sum observed, or reappearance of any lesion that had disappeared, or clear worsening of any assessable disease, or appearance of any new lesion or site.	Disease was evaluated every 2 months during the first year and included a repeat CT scan or MRI to confirm response in 4 weeks. Patients were planned to be seen every 3 months for the second and third year and every 6 months thereafter.
Japan-91[18]	Response after the radiation therapy course was defined as complete if all clinically and radiographically detectable malignant disease had disappeared completely 3 months after the end of treatment. Treatment failure was indicated by persistent disease and/or the appearance of new lesions or disease progression. Early death from any cause, including toxic death, was considered uncontrolled locoregional disease in the statistical analysis. The persistence of radiologic signs of nasopharyngeal mucosal thickening was scored as a partial response, even when all other disease sites had responded completely.	
TCOG-94[19]	Progressive disease was defined as the growth of any measurable lesion, according to CT or MRI, by more than 25% of the sum of two perpendicular diameters, or as the presence of palpable lesions or the appearance of any new lesion or site.	
PWHQEH-94[20]		Patients were seen every 8 weeks in the fi rst year, every 12 weeks in the second and third years, and every 16 – 24 weeks thereafter
QMH-95[21]	Complete remission was defined as no histologic evidence of disease in the NP or neck node at 12 weeks after completion of RT.	At 6 weeks and 8 weeks after completion of RT, nasopharyngoscopy and multiple biopsies were performed to assess the disease status in the NP. CT scan of the NP and neck was performed at 3 months after completion of RT. Residual neck nodes were evaluated by ultrasound-guided aspiration biopsy. […] patients were followed up every month during the first year, every 2 months in the second year, and then every 3 to 6 months afterwards. Follow-up nasopharyngoscopy and CT scan were performed every 6 months for the first 2 years and thereafter when clinically indicated.
VUMCA-95 (unpublished)		
SQNP01[22]		the trial patients were observed every 4 months for the first year, every 6 months for the subsequent 2 years, and annually thereafter.
NPC-9901[23]	For statistical purposes, persistent primary or nodal disease at 16 weeks after completion of RT was defined as locoregional failure […] The earliest dates of detecting tumor relapse at	The first assessment of tumor response was performed 6–16 weeks after completion of radiotherapy. All patients were assessed by complete physical examination and fiberoptic

Trial	Definition of progression	Frequency of FU visits
	different sites were recorded.	nasopharyngoscopy. Further investigations were performed with computed tomography or magnetic resonance imaging and other tests when indicated.[…]. Patients were re-assessed at least every 3 months during the first 3 years and then every 6 months thereafter until death.
NPC-9902[24]	For statistical purpose, persistent primary or nodal disease at 16 weeks after completion of RT was taken as locoregional failure.	The first assessment of tumor response was performed 6–16 weeks after the completion of RT
Guangzhou 2001[25]	Regional recurrences were diagnosed by clinical examination of the neck and, in doubtful cases, by fine-needle aspiration or CT scan of the neck.	
NPC008[26]	Tumor response to neoadjuvant therapy was evaluated before commencement of CRT by nasopharyngoscopy, physical examination, and CT scan. Tumor response after CRT was evaluated by nasopharyngoscopy and biopsy, physical examination, and CT scan at 6 weeks after completion of CRT. Tumor response was classified according to WHOresponse criteria.[32]	Patients were followed up every 3 months in the first 2 years, then every 6 months in the third and fourth year, and yearly thereafter
Guangzhou 2002-02[27]	The evaluation of efficacy was performed according to the WHO standard[32]	
Guangzhou 2002-01[28]	Progressive bone erosion or soft-tissue swelling were considered signs of local recurrence. Regional recurrences were diagnosed by clinical examination of the neck, and irresolute cases were confirmed by fine needle aspiration or MRI or intensive CT of the neck.	After the completion of treatment, patients were evaluated at least once every 3 months during the first 3 years and then every 6 months thereafter until death. Nasopharyngoscopy, MRI of the head and neck, chest radiography, and abdominal sonography were routinely performed annually or at the time of the clinical suggestion of tumor relapse.
Guangzhou 2003[29]	Tumor response was evaluated by physical examination, nasopharyngoscopy, and MRI of the head and neck at 3 months after the completion of RT. Tumor response was classified according to the WHO response criteria[32]. A complete response was defined as the complete disappearance of all objective evidence of disease, which was confirmed by physical examination, direct nasopharyngoscopy, and MRI.	
HeCOG[30]	Response was assessed centrally according to the World Health Organization criteria	
Shanghai[4,&]	Follow-up assessments included physical examination, MRI of the nasopharynx, ultrasound of the abdomen and chest X-ray/CT.	Patients were assessed before being randomly assigned, every week during treatment, and 3 months after completion of therapy, then every 3 months for the first and second year, every 6 months during the year 3–5, and yearly after 5 years.
Guangzhou 2006[31]	All local recurrences were diagnosed with fibreoptic endoscopy and biopsy, MRI scan, or both, of the nasopharynx and the skull base showing progressive bone erosion and soft tissue swelling. Regional recurrences were diagnosed by clinical examination of the neck and, in doubtful cases, by fi ne needle aspiration or an MRI scan of the neck	Participants were assessed every 3 months during the first 3 years, and every 6 months thereafter until death.