RESEARCH ARTICLE

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# Improved Overall Survival Due to Reduced Waiting Time in Nasopharyngeal Cancer Patients Treated with Chemoradiotherapy in Yogyakarta, Indonesia

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## Abstract

**Background:** In Indonesia, nasopharyngeal carcinoma (NPC) is highly prevalent and is one of the leading causes of cancer-related mortality. Lower overall survival (OS), compared to neighboring countries, is associated with a prolonged waiting time (WT) and overall radiotherapy (RT) treatment time (OTT). In 2018, the RT department of the Dr. Sardjito Hospital in Yogyakarta, Indonesia, increased the number of treatment machines and clinical staff. This may have led to an improvements in WT and OTT. Therefore, we analyzed a recent cohort of NPC patients to evaluate the outcomes in light of these changes. **Materials and Methods:** A retrospective cohort of 229 NPC patients underwent chemoradiotherapy with curative intent between January 2018 and December 2021. The majority had locally advanced NPC. The turning point was in 2018, marking a pivotal year. Consequently, the years 2019-2021 were compared with 2018. Endpoints included WT, OTT, OS, as well as locoregional control (LRC) and disease-free survival (DFS). **Results:** The mean follow-up time was 16.9 months. For all patients, the median WT and OTT were 110 days and 50 days. Comparing 2018 with 2019-2021, the WT differed significantly with 190 versus 97 days ($p<0.001$) while the OTT, 53 versus 50 days, was borderline different ($p=0.049$). The 2-year OS significantly improved from 42.6% in 2018 to 60.5% among patients treated between 2019-2021 ($p=0.042$). **Conclusion:** In conclusion, this study analyzed the impact of WT and OTT on outcomes for NPC patients undergoing chemoradiotherapy at Dr. Sardjito Hospital. A significant decrease in WT of 97 days was observed when compared to 2018. However, the limited availability of advanced imaging likely resulted in an underestimation of distant metastases, leading to a 2-yr OS of 60.5%. Better staging methods, as well as improved awareness of NPC, are crucial for better treatment decisions and improving future patient outcomes.

**Keywords:** Nasopharyngeal cancer- chemoradiotherapy- waiting time- overall survival- Indonesia

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## Introduction

Nasopharyngeal carcinoma (NPC) is a frequently diagnosed cancer in Indonesia with an estimated incidence of 6.2 per 100,000 inhabitants leading to 17,000 new patients per year, while the incidence in Europe is between 0.2-0.4 per 100,000 inhabitants [1, 2]. This difference in geographical distribution strongly suggests specific risk factors, such as the Epstein-Barr virus and environmental factors [2, 3]. NPC is very sensitive for radiotherapy (RT) and patients generally have a good prognosis [4]. Early-stage NPC can be cured with RT alone, while advanced stage NPC needs a combination with chemotherapy. Patients with stage III-IV have a 3-year disease-free survival (DFS) of 70-80% when treated with concurrent chemo-radiotherapy [5 ,6].

However, previous publications demonstrated lower survival rates in NPC patients treated in the Dr. Sardjito hospital in Yogyakarta, Indonesia, revealing a 5-year overall survival (OS) rate of 38.6%, although the rate increased to 71.0% in patients with a complete response [4, 7]. Possible reasons for these different survival rates were the waiting time (WT) between diagnosis and start of treatment as well as the overall RT treatment time (OTT) of the (chemo)radiotherapy. In 2016, lead times were investigated at the radiotherapy department of the

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same hospital in Yogyakarta [8]. In total, 142 NPC patients were treated with (chemo)radiotherapy with curative intent between March 2009 and May 2014. The median WT for the first RT treatment was 117 days and the median OTT was 58 days. The OTT was prolonged due to interruptions of the RT, but was not associated with a poor clinical outcome. However, a relatively shorter WT was found to be associated with therapy outcome: patients with a WT of 101 days had a higher chance on a complete response than patients with a WT of 140 days. In addition, a prolonged WT was associated with a lower locoregional control as well as DFS. For all patients, the 2-year OS was 58%.

In recent years, several (logistical) adjustments were implemented leading to improved pathways at the RT department of the Dr. Sardjito hospital in Yogyakarta. One major improvement was that the department expanded its number of linear accelerators (linac) from two to three in 2018. In addition, the working hours were expanded as well as the number of patients treated per linac. Also, the clinical staff and the medical physicists doubled in number. However, the introduction in 2014 of a national health care insurance had an unintended consequence of a substantially increase of the WT for RT. Due to the improved access to healthcare, more patients became eligible for RT.

From 2018, the WT decreased dramatically, starting with 24 months in 2017 to 1.5 months at the end of 2018 leading to a further decrease of 2 weeks in 2021. Furthermore, the radiation technique changed from two-dimensional (2D) and three-dimensional (3D) RT to intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) from 2018 and onwards. These improvements may have resulted in a better outcome of NPC patients. The aim of this study was to compare a recent cohort of patients treated between January 2018 and December 2021. Since adjustments were implemented in 2018 ultimately leading to an impressive WT of 2 weeks in 2021, the year 2018 was compared with 2019-2021. The primary endpoints were WT, the OTT and OS and in addition, DFS and locoregional control (LRC) were investigated.

## Materials and Methods

*Patient selection*

A retrospective study was performed including 374 NPC patients who were treated at the department radiation oncology of the Dr. Sardjito hospital, Gadjah Mada University, Yogyakarta, Indonesia, between January 2018 and December 2021. Relevant patient and tumor characteristics, treatment data and (electronic) medical records were collected retrospectively. Standard work-up consisted of a diagnostic computed tomography (CT)-scan of the nasopharynx, an ultrasound of the liver, an X-thorax and a bone survey. A biopsy of the primary tumor and/or involved lymph nodes of the neck was performed to confirm NPC (World Health Organization type 1, 2 or 3). Patients were staged according to the 8th edition of the American Joint Committee on Cancer (UICC/AJCC).

Treatment response, the date of recurrence (local, regional and distant), the last date of follow-up and the date of death if applicable were recorded. If the patients' last visit to the hospital was more than 6 months ago, the patient or family was called or visited at home to inquire about the patients' current condition. Patients were excluded if the patient had: distant metastases at diagnosis (N=17), received a palliative dose or very low dose due to discontinuation (N=42), missing diagnostic CT-scan (N=14), treated for a recurrence (N=23), a diagnosis other than NPC WHO type 1-3 (N=16), did not start the radiotherapy (N=28) or had missing (electronic) medical record (N=5). The study protocol was approved by the ethical board of the Dr. Sardjito hospital.

*Radiotherapy preparation*

Patients were treated with external beam radiotherapy (2D, 3D, IMRT or VMAT). The primary tumor as well as involved lymph nodes were treated to a dose of 60 Gy (stage I) or 70 Gy (stage II-IV). Uninvolved lymph nodes were treated to an elective dose of 46 Gy. The radiotherapy was given once daily, 5 times a week. For treatment planning, a 3D planning CT-scan with intravenous contrast was acquired for all patients. Fixation material for the head, neck and shoulders were used. The CT-scan was used to delineate the gross tumor volume (GTV) of the primary tumor, the involved LNs and organs at risk (OARs). To take into account microscopical spread, a margin of 5 mm was added for the clinical tumor volume (CTV). Lastly, an additional margin of 3-5 mm was used for the planning target volume (PTV). The following OARs were contoured according to departmental protocol: the parotid and submandibular glands, the brain stem and spinal cord, the oral cavity, the eyes and optic nerves including the chiasm and the temporal lobes.

The treatment plans were designed with 6/10-MV photons. Dose distributions were calculated using Monaco version 5.11. Treatment verification was done with Electronic Portal Imaging Device (EPID) dosimetry. In case of significant anatomical changes, such as weight loss or tumor regression, re-planning was considered. Almost all patients received chemotherapy with various regimens.

*Treatment outcome and endpoint definition*

The WT was calculated from the day of diagnosis (date of pathological confirmation) until the first day of radiotherapy. The OTT was calculated from the first day until the last day of the radiotherapy. The follow-up time was calculated from the first day of radiotherapy until date of death or last visit to the hospital.

The primary endpoints were: WT, OTT and OS (calculated from first day of radiotherapy until the day of death of last follow-up). Other endpoints were: therapy response, locoregional control (calculated from last day of radiotherapy until the day of local and/or regional recurrence) and DFS (calculated from last day of radiotherapy until the day of any recurrence). All endpoints were calculated for the study group as a whole, but since 2018 was marked as a turning point, the year 2018 was compared with 2019-2021 as well.

*Statistical analysis*

Patient and tumour characteristics were presented

using either the mean (+ standard deviation, SD) or the median (+interquartile range, IQR). The independent samples T-test was performed to compare characteristics and in case of a normal distribution. Kaplan-Meier survival curves were plotted for each primary endpoint. The cohorts 2019 and 2019-2021 were compared using the independent samples T-test. P-values <0.05 were considered statistically significant. All analyses were conducted using the SPSS software, version 28 for Apple (IBM®).

## Results

*All patients*

Two hundred and twenty-nine patients were eligible for this retrospective study. The mean follow-up time was 16.9 months (SD, 12.8). The majority of the patients (75.1%) had an advanced stage III or IVA. Chemotherapy was administered in 99% of all patients. The median WT was 110 days (IQR, 64-185) and the median OTT was 50 days (IQR, 48-56). Other patient, tumour characteristics and time variables are shown in Table 1A and 2A.

*Primary endpoints*

*Therapy response*

The response after the radiotherapy was available for 141 patients. In 110 patients, a complete response was observed and in 31 patients an incomplete response. There was no difference in the OTT, being 53 days in both groups. The median WT showed a no significant difference: patients with a complete response had a median WT of 102 days versus 111 days in the incomplete response-group (P=0.716).

*Locoregional control*

LRC was available for 187 patients showing 23 events. The median time to LRC was not reached, but the mean time was 41.1 months (SD, 1.5). The 2-year and 3-year LRC was 80.3% and 75.9%, respectively.

*Disease-free survival*

The DFS could be analysed in 185 patients with 62 events. The median time to DFS was not reached, but the mean time was 30.2 months (SD, 1.9). The 2-year and 3-year DFS was 59.1% and 47.4%, respectively.

*Overall survival*

The overall survival was available for 227 patients with 93 events. The median time to OS was 34.0 months (95% CI, 21.7-46.3). The 2-year and 3-year OS was 56.3% and 47.2%, respectively. LRC, DFS and OS are shown in Figure 1A-C.

*Comparison between 2018 and 2019-2021*

Patient and tumor characteristics between 2018 and 2019-2021 are shown in Table 1B. The number of patients treated in 2018 was 48 (21.0%) while 181 (79.0%) patients were treated between 2019-2021. In 2018 the WT was 190 days, which was significantly different with the WT of 97 days in 2019-2021 (p=<0.001) (Table 2B). The OTT did not differ significantly, being 53 days versus 50 days (p=0.049). The OS at 1 and 2 years differed significantly between the two groups, respectively 63.8% vs. 93.3%, and 42.6% vs. 60.5% (p=0.042) (Figure 2A-C). There were no differences observed between therapy response, locoregional control and DFS.

Table 1A. The Patient and Tumor Characteristics of the 229 NPC Patients Treated with Curative Intent between 2018 and 2021 at the Dr. Sardjito Hospital, Yogyakarta, Indonesia.

| Characteristic | Absolute (relative) number |
|---|---|
| Median age (IQR) | 50 years (42-59) |
| Gender | |
| Male | 159 (69.4%) |
| Female | 70 (30.6%) |
| T-stage | |
| Tx | 1 (0.4%) |
| T1 | 37 (16.2%) |
| T2 | 78 (34.1%) |
| T3 | 54 (23.6%) |
| T4 | 59 (25.8%) |
| N-stage | |
| N0 | 33 (14.4%) |
| N1 | 59 (25.8%) |
| N2 | 98 (42.8%) |
| N3 | 39 (17.0%) |
| TNM-stage | |
| I | 7 (3.1%) |
| II | 49 (21.4%) |
| III | 87 (38.0%) |
| IVA | 86 (37.6%) |
| Histology | |
| Non-keratinizing SCC, undifferentiated | 210 (91.7%) |
| SCC, moderately/poorly differentiated | 6 (2.6%) |
| Other | 4 (3.5%) |
| Missing | 9 (3.9%) |
| Chemotherapy | |
| Neoadjuvant | 34 (14.8%) |
| Concurrent | 110 (48.0%) |
| Neoadjuvant+concurrent | 55 (24.0%) |
| Neoadjuvant+Concurrent+adjuvant | 1 (<0.1%) |
| Concurrent+adjuvant | 8 (3.4%) |
| Neoadjuvant+adjuvant | 1 (<0.1%) |
| Adjuvant | 2 (0.1%) |
| No chemotherapy | 6 (2.6%) |
| Unknown/missing | 12 (5.2%) |
| Radiotherapy technique | |
| 2D | 45 (19.7%) |
| 3D | 10 (4.4%) |
| IMRT | 173 (75.5%) |
| VMAT | 1 (0.4%) |

IQR, interquartile range; SCC, squamous cell carcinoma; 2D, two-dimensional; 3D, three-dimensional; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.

Table 1B. The Patient and Tumor Characteristics of the NPC Patients Treated with Curative Intent in 2018 (N=48) versus 2019-2021 (N=181) at the Dr. Sardjito Hospital, Yogyakarta, Indonesia.

| Characteristic | | 2018 (N=48) | 2019-2021 (N=181) | P-value |
|---|---|---|---|---|
| Median age (IQR) | | 50 years (41-62) | 50 years (42-58) | 0.615 |
| Gender | Male | 35 (72.9%) | 124 (68.5%) | 0.558 |
| | Female | 13 (27.1%) | 57 (31.5%) | |
| T-stage | Tx | 1 (2.1%) | 0 | 0.032 |
| | T1 | 11 (22.9%) | 26 (14.4%) | |
| | T2 | 16 (33.3% | 62 (34.3%) | |
| | T3 | 13 (27.1%) | 41 (22.7%) | |
| | T4 | 7 (14.6%) | 52 (28.7%) | |
| N-stage | N0 | 11 (22.9%) | 22 (12.2%) | 0.002 |
| | N1 | 19 (39.6%) | 40 (22.1%) | |
| | N2 | 13 (27.1%) | 85 (47.0%) | |
| | N3 | 5 (10.4%) | 34 (18.8%) | |
| TNM-stage | I | 4 (8.3%) | 3 (1.7%) | 0.002 |
| | II | 15 (31.3%) | 34 (18.8%) | |
| | III | 17 (35.4%) | 70 (38.7%) | |
| | IVA | 12 (25.0%) | 74 (40.9%) | |
| Histology | Non-keratinizing SCC, undifferentiated | 41 (85.4%) | 169 (93.4%) | <0.001 |
| | SCC, moderately/poorly differentiated | 4 (8.4%) | 2 (1.1%) | |
| | Other | 1 (2.1%) | 3 (1.7%) | |
| | Missing | 2 (4.2%) | 7 (3.9%) | |
| Chemotherapy | Neoadjuvant | 19 (39.6%) | 15 (8.3%) | 0.703 |
| | Concurrent | 8 (16.7%) | 102 (56.4%) | |
| | Neoadjuvant+concurrent | 13 (27.1%) | 42 (23.3%) | |
| | Neoadjuvant+Concurrent+adjuvant | 0 | 1 (0.6%) | |
| | Concurrent+adjuvant | 0 | 8 (4.4%) | |
| | Neoadjuvant+adjuvant | 1 (2.1%) | 0 | |
| | Adjuvant | 0 | 2 (1.1%) | |
| | No chemotherapy | 2 (4.2%) | 4 (2.2%) | |
| | Unknown/missing | 5 (10.4%) | 7 (3.9%) | |
| Radiotherapy technique | 2D | 31 (64.6%) | 14 (7.7%) | <0.001 |
| | 3D | 7 (14.6%) | 3 (1.7%) | |
| | IMRT | 10 (20.8%) | 163 (90.1%) | |
| | VMAT | 0 | 1 (0.6%) | |

IQR, interquartile range; SCC, squamous cell carcinoma; 2D, two-dimensional; 3D, three-dimensional; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.

## Discussion

This study investigated whether WT and OTT was associated with outcome in NPC-patients treated with (chemo)radiotherapy at the Dr. Sardjito hospital in Yogyakarta, Indonesia. Expansion of staff and treatment machines as well as the implementation of modern radiation techniques were applied in 2018, which was marked as a turning point year. Therefore, the patients treated in 2018 were compared with the patients treated between 2019-2021. The results demonstrated a significantly decreased WT of 190 days versus 97 days,

Table 2A. Time Variables for All 229 NPC Patients Treated with (Chemo)radiotherapy

| Variable | Days (median, IQR) | Days (mean, SD) |
|---|---|---|
| Waiting time (date of diagnosis to first day of RT) | 110 (64-186) | |
| Overall treatment time (from first to last day of RT) | | 53.1 (9.6) |
| Time from pCT to first day of RT | | 23.5 (15.0) |
| Time from last day of RT to date of response evaluation | 96 (69-112) | |

IQR, interquartile range; SD, standard deviation; pCT, planning-CT-scan; RT, radiotherapy

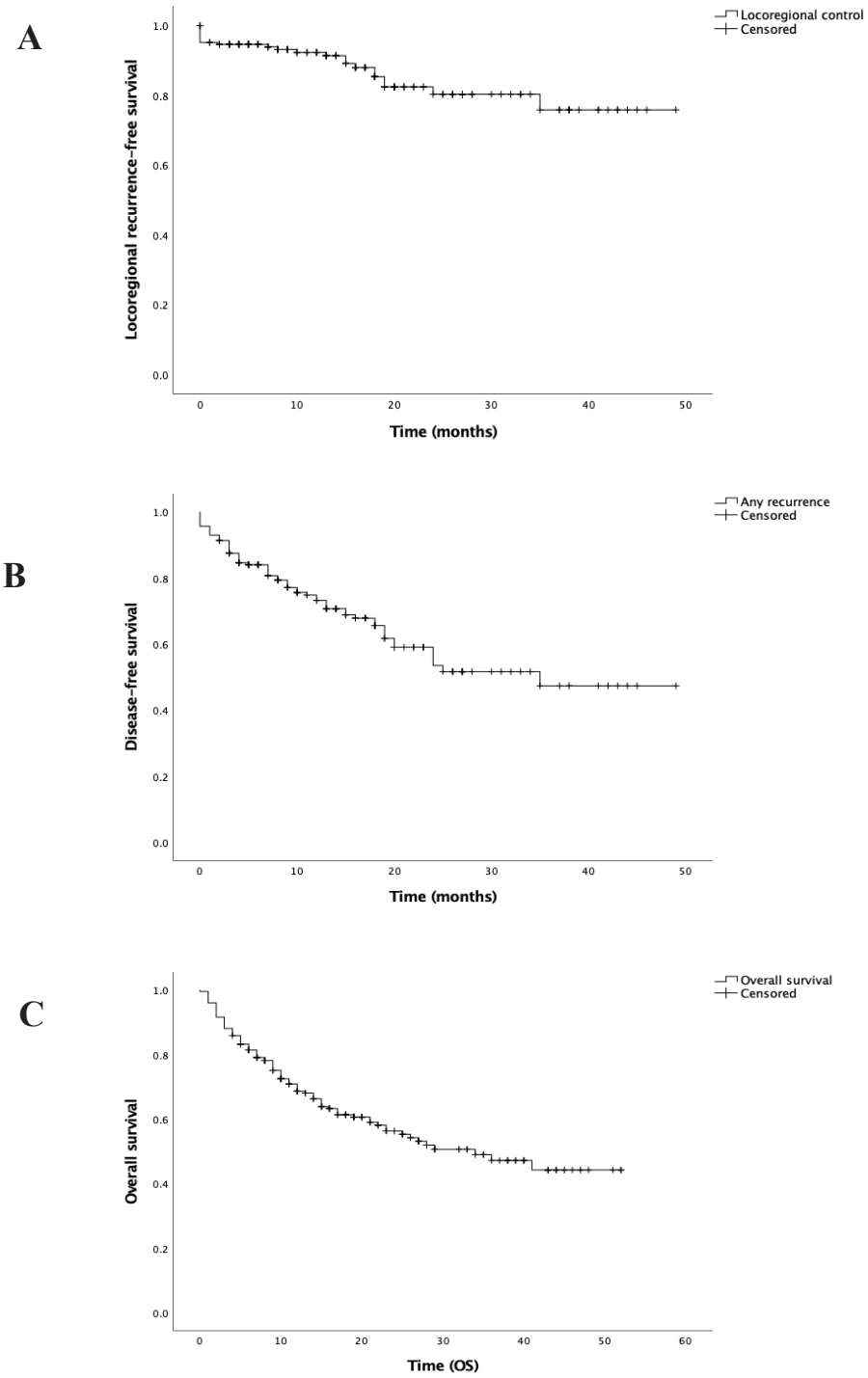


Figure 1. A-C. Locoregional Recurrence-Free Survival, Disease-Free Survival and Overall Survival for the 229 NPC Patients

resulting in an improved 2-year OS of 42.6% versus 60.5% (p=0.042) despite the imbalance between the two cohorts showing more patients with a higher T-stage and N-stage in the 2019-2021 cohort (Table 1B).

The association between the radiotherapy WT and treatment outcomes for patients with head and neck

Table 2B. Time Variables for the NPC Patients Treated with (Chemo)radiotherapy in 2018 Compared with 2019-2021

| Variable | 2018 (N=48) | 2019-2021 (N=181) | P-value |
|---|---|---|---|
| Waiting time (date of diagnosis to first day of RT) – days (median, IQR) | 190 (127-255) | 97 (55-164) | <0.001 |
| Overall treatment time (from first to last day of RT) – days (mean, SD) | 56 (13) | 52 (8) | 0.049 |
| Time from pCT to first day of RT – days (median, IQR) | 22 (18-29) | 19 (14-29) | 0.977 |
| Time from last day of RT to date of response evaluation – days (median, IQR) | 101 (67-114) | 95 (69-112) | 0.769 |

IQR, interquartile range; SD, standard deviation; pCT, planning-CT-scan; RT, radiotherapy

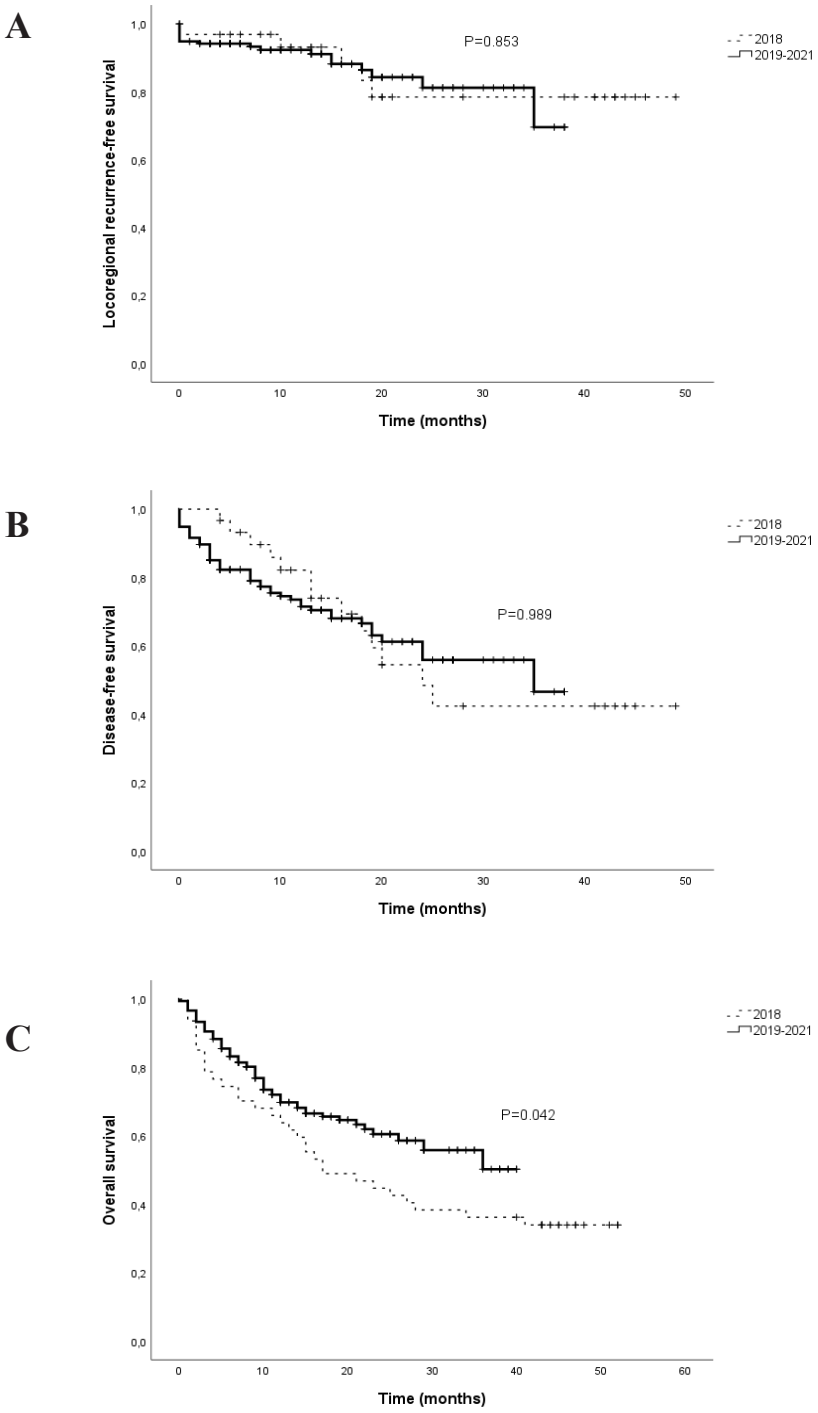


Figure 2. A-C. Locoregional Recurrence-Free Survival, Disease-Free Survival and Overall Survival for the Patients Treated in 2018 (N=48) versus 2019-2021 (N=181).

cancer has long been recognized. Two systematic reviews confirmed that a prolonged WT was associated with higher risk of local recurrence rates resulting in a lower OS [9, 10]. Both reviews advocated that delays in starting with RT should be minimized. The current analysis has shown that the year 2018 did indeed mark a turning point, as various improvements in the RT department resulted in a better WT and OTT. Two analyses have demonstrated that the WT and OTT before 2018 were indeed much longer. Stoker et al. analysed 142 NPC patients treated with chemoradiotherapy at the RT department of the Dr. Sardjito Hospital between 2009-2014 showing a median WT and OTT of 120 days and 58 days, respectively [8]. Additionally, similar long WT and OTT were found for patients who were treated for breast cancer at the same department [11]. It is remarkable that the RT department was able to implement various adjustments in the year 2018. This included expanding the number of LINACs from two to three and reducing the number of patients treated per LINAC per day, resulting in fewer technical malfunctions possibly contributing to the improved OTT [12].

A noteworthy outcome was the improvement in survival within the cohort of 2019-2021. The 2-year OS increased from 42.4% to 60.5%, which was very likely the result of the improved WT of 190 days versus 97 days. However, when analysing all patients together, the OS did not improve compared to the results by Stoker et al., showing a 2-year OS of 56.3% versus 58% (Figure 1C). The most likely explanation is that the staging procedures have remained unchanged. To rule out distant metastases, the patients underwent an X-thorax, an ultrasound of the liver and a bone survey. 18Fluoro-deoxyglucose-positron emission tomography (18F-FDG-PET)-scans are not yet available in the Dr. Sardjito hospital, although these scans are the preferred method to exclude metastases [13, 14]. The nearest hospitals where patients can undergo 18F-FDG-PET-scans are in Jakarta and Bandung where only a minority has the opportunity to go. It is plausible that part of the patients already had metastases, given the often significant extent of the disease (cT4 and/or cN3 showing an extensive intracranial growth or very large lymph nodes). Despite the fact that patients who were treated in the Dr. Sardjito hospital did not yet have access to 18F-FDG-PET-scans, it is worthwhile mentioning that the nuclear department recently installed a bone scan. This will allow patients to undergo a more accurate staging procedure.

Despite the LRC and DFS not differing between the two cohorts (Figure 2A-B), there was a large difference with Stokers' earlier analysis, being 48% versus 80%% (2-year LRC) and 32% versus 59% (2-year DFS), respectively. The most likely cause for this, besides the impressive improvement of WT, is the introduction of diagnostic MRI-scans since 2017. MRI-scans are essential when contouring the primary tumor in the nasopharynx due to their high ability of distinguishing soft tissue [1, 15, 16]. It is plausible that this resulted in an improved LRC and DFS for patients treated between 2018-2021 when compared with 2009-2014. In addition, the RT department implemented modern RT techniques in later years (Table 1B). The majority of the NPC patients were treated with IMRT and VMAT resulting in less higher toxicity rates due to a better sparing of organs at risk without compromising LRC and OS [17-19].

However, alongside advanced imaging and RT techniques, it is crucial that the knowledge of general practitioners and supporting staff in primary care regarding NPC is sufficiently robust. Awareness of this disease is key, which was confirmed by Fles et al, leading to minimization of doctors' delay [20]. Furthermore, it is recognized that patients' limited awareness of NPC often translates into a six-month delay in seeking medical care after the onset of symptoms [21]. The importance of awareness is underscored by the fact that patients in cohort 2019-2021 were diagnosed at more advanced stages, likely due to a delay in diagnosis. Therefore, awareness and ultimately prevention are essential components in the treatment of NPC.

We acknowledge the limitations of this observational study, as it involves retrospective analysis. The absence of a centralized database system in Indonesia resulted in a significant amount of missing data. In our analysis, a considerable portion of patients had appointments less than four months ago at the head-and-neck department or radiotherapy department. For patients who visited the outpatient clinic more than four months ago, the research team either contacted them by phone or conducted home visits. In the end, all patients were successfully traced resulting in a reliable outcome for OS. However, the number of patients with locoregional and distant metastases was likely underestimated. The communication of patient diagnoses and treatment outcomes between hospitals has been insufficient to date, thus the responsibility for sharing information rests with the patients. Consequently, there is limited access to comprehensive patient information across multiple healthcare facilities.

In conclusion, this study analysed the impact of waiting time and overall treatment time on the outcomes for NPC patients undergoing (chemo)radiotherapy in the Dr. Sardjito hospital, Yogyakarta, Indonesia. There has been a notable improvement in recent years compared to the pivotal year of 2018, leading to a significant increase of the 2-year OS of 60.5%. Reasons for this were partly due to the expansion in staff and treatment machines. However, the limited availability of advanced imaging probably resulted in an underestimation of distant metastases. The implementation of more accurate staging methods, such as 18F-FDG-PET scans, early detection and improved awareness of NPC as well as improved referral pathways are crucial for better treatment decisions and improving future patient outcomes.

## Author Contribution Statement

All authors contributed to this analysis through conceptualization, data analysis, writing, and review. The study protocol was approved by the ethical board of the Dr. Sardjito hospital, Gadja Mada University, Yogyakarta, Indonesia.

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The research data are available from the authors. The study was not registered in registration database.

*Conflict of interest*

None.

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