



## Photodynamic Therapy As an Adjuvant Therapy for Local-Partial Remission of Nasopharyngeal Carcinoma After Standard Therapy in Sardjito Hospital Yogyakarta A Five-Year-Overall Survival Rate Analysis Study

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### ABSTRACT

**Background:** The foremost problems of nasopharyngeal carcinoma (NPC) management are high loco-regional remission, local recurrence and spreading rate post therapy. Photodynamic therapy (PDT) has been done for treatment of tumors less than 1 cm in size and depth in a very difficult location, where radical excision by surgery was not possible. The aim of this study is determining 5-year-overall survival rate of local-partial remission of NPC after standard therapy followed by additional PDT.

**Method:** The survival study is subjected to the 5 years-overall survival rate of local-partial remission. Photosensitizer (Foscan<sup>R</sup>) 0,15mg/kgBW was injected to NPC patients and followed by 20 joule/cm<sup>2</sup>, 642 wave length and 100 watts/cm<sup>2</sup> irradians non thermal laser illumination 96 hours after injection. The PDT result was confirmed with biopsy, CT scan, upper abdominal USG, thoracic radiograph and bone survey for 12 weeks after treatment. Follow up was done every 3 months in first year, continued every 6 months in the second year, and followed once a year. The sample collected from January 2005 to December 2010, and 33 cases met the inclusion and exclusion criterias, but only 20 cases were eligible inclusion criteria. The 5 years-overall survival was defined as the time from diagnosis to death from any cause or last follow up, calculated by Kaplan Meier survival analysis.

**Results:** The 5-year-overall survival rate was 50%.

**Conclusion:** PDT as an additional treatment for small local-partial remission in NPC post treatment is an alternative therapy to improve the treatment outcome and survival rate.

**Keywords:** NPC, PDT, 5-year-survival rate

### ABSTRAK

Photodynamic therapy sebagai terapi ajuvan karsinoma nasofaring remisi lokal-parsial setelah terapi standar di RSUP Dr. Sardjito Yogyakarta: Studi analisis angka kehidupan lima tahun

**Latar belakang:** Problem utama terapi standar karsinoma nasofaring (KNF) adalah rendahnya angka keberhasilan terapi, terutama adanya remisi parsial, baik pada tumor primer maupun metastasis. Photodynamic therapy (PDT) telah digunakan untuk pengobatan tumor di superfisial, dengan diameter kurang dari 1 cm, terutama pada tumor yang letaknya tersembunyi dan sulit dioperasi secara radikal. Penelitian ini bertujuan menentukan angka kehidupan 5 tahun pada penderita KNF dengan remisi parsial pada tumor primernya, setelah diterapi secara standar dan dilakukan PDT sebagai terapi tambahan.

**Metode:** Studi analisis kesintasan terhadap kehidupan 5 tahun penderita KNF yang mengalami remisi lokal-parsial setelah terapi standar dan PDT. Photosensitizer (Foscan<sup>R</sup>) 0,15mg/kgBW diinjeksikan pada penderita KNF, dan setelah 96 jam, dilanjutkan dengan irradians non thermal laser illumination sebesar 20 joule/cm<sup>2</sup>, panjang gelombang 642 dan 100 watts/cm<sup>2</sup>. Hasil PDT dikonfirmasi dengan biopsi, CT scan, USG abdomen, rontgen thoraks dan bone survey pada 12 minggu setelah terapi. Tahun pertama, dilakukan follow up setiap 3 bulan, di tahun kedua setiap 6 bulan, dan selanjutnya setiap setahun sekali. Sampel didapat dari Januari 2005 sampai Desember 2010, dimana 33 pasien KNF post PDT memenuhi kriteria inklusi dan eksklusi, namun hanya 20 pasien yang memenuhi kriteria inklusi 5-tahun-follow up. Angka kehidupan 5 tahun ditentukan berdasarkan saat diagnosis sampai kematian penderita, atau sampai follow up terakhir, dihitung dengan analisis kesintasan Kaplan Meier.

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**Hasil:** Angka kehidupan keseluruhan selama 5 tahun adalah 50%.

**Simpulan:** PDT sebagai tambahan terapi terhadap KNF yang

mengalami remisi parsial paska terapi standar dapat digunakan sebagai terapi alternatif terhadap KNF yang mengalami remisi parsial paska terapi standar.

## INTRODUCTION

Nasopharyngeal carcinoma is the most frequent malignancy among head and neck malignancies, especially in male population. It has different clinical characteristics from other head and neck malignancies in which it is very invasive and may undergo rapid metastasis.<sup>1,2</sup>

The epidemiology of NPC is quite unique and distinct from other malignant tumors arising from head and neck. In Europe and USA, NPC is an uncommon type of tumor. However, NPC is more common among Southeast Asia countries, Southern Chinese and some of African population. The highest incidence of NPC can be found in province of Guangdong, Southern China with 40-50 new cases per 100.000 population per year. The early stage of NPC symptoms are unspecific, causing NPC patients to present advance stage, which therefore result in unsatisfactory therapy outcome.<sup>1,3</sup>

Currently the main modality of early NPC therapy is radiotherapy. The foremost problems are, loco-regional partial remission, local recurrent rate, and spread after radiotherapy remain high, which was around 18%-45%.<sup>4,5</sup> In advanced stage, NPC is treated with a combination of radiotherapy and chemotherapy. Chemotherapy can be given before radiotherapy (neoadjuvant chemotherapy), or after radiotherapy (adjuvant chemotherapy), or simultaneously (concurrent chemotherapy). The aims of additional chemotherapy are to decrease the loco-regional recurrence and distant metastasis, as well as to increase disease free or overall survival. The main problem in NPC partial result after full dose treatment is the additional treatment. Re irradiation/chemotherapy need waiting time to overcome the damage of normal tissues and side effects of radio and chemotherapy.<sup>6</sup> Up until now the treatment option for recurrent and persisten NPC are limited.

The study of Lee, *et al.* reported that early stage NPC patients who underwent radiotherapy, had completed remission by 80-90%, and the 5-year-overall survival rate was higher. However, for the late stage patients, it dramatically dropped to 10-40%. If distant metastasis was present, 85% of NPC patients would die in the first year.<sup>7</sup>

The therapeutic success rate for NPC in each domestic and International Centre or Hospital are variated.<sup>1,6,8</sup> The presence of distant metastasis before therapy, partial-local (uncomplete) remission and recurrences after therapy is an important factor for the therapy success rate.

Photodynamic therapy (PDT) is a method of local cancer treatment based on administration of photosensitizing substance selectively absorbed by tumor cells which lead after exposure to optical radiation, to tumor destruction.<sup>9</sup> Photodynamic therapy is clinically approved, minimal invasive therapeutic procedure that can exert a selective cytotoxic activity toward malignant cells.<sup>10</sup>

The use of PDT in NPC treatment is relatively new, and has been used for superficial, less than 1 cm in depth and less than 3 cm in size in both benign and malignant tumors since 1980, i.e. those with very difficult locations where surgery approach for radical excision was not possible. The mechanism of PDT is an interaction among laser, molecular oxygen and sensitizer agent. Photo sensitizer causes laser energy to be absorbed by tumor tissue, which eventually makes the tumor tissue damaged and undergo necrosis. PDT can be done more than one time in the short periode, and not necessary to wait in long time.<sup>11,12</sup>

Photo sensitizer injected into the body will become active when it is interacting with molecular oxygen, and thus produce singlet oxygen, which is followed by bio molecular reaction, as well as performing cytotoxic products that causes cell and tissue damages. Photo sensitizer also reacts directly with cell and produces free radicals.<sup>10,12</sup>

Additional action of PDT in tumor therapy is making thrombus in tumor vascularization through thromboxane production, which may result in hypoxia or anoxia, thus leading to cell death. Photodynamic therapy can also strengthen apoptosis process by inducing cytochrome-C production from mitochondria to cytoplasm.<sup>10</sup>

The objective of the study is to determine 5 year-overall survival rate of local-partial remission of NPC patients post standard therapy who received additional PDT.

## METHOD

This was an survival analysis study with retrospective design. Five-year-overall survival was defined as the time from diagnosis to death from any cause or lost of follow up. The zero point was the time of NPC diagnosed, the end point of the study was death in 5 years during follow up, which was calculated by the Kaplan Meier survival method. The standard NPC therapy in Sardjito Hospital is radiotherapy 6600-7000 Cgy forearly stage. Neo adjuvant chemotherapy (*Cis platinum combined with 5 flurouracyl*) is administered

for advanced stage. Sample collection started from January 2011, retrospectively.

In Sardjito Hospital Yogyakarta, phase II PDT study has been done since 2005. The inclusion criteria were local-partial remission, tumor volume not more than 1 cm<sup>3</sup>, absence of regional and distant metastasis confirmed with biopsy, CT Scan, upper abdominal USG, liver function test, Ro thorax, and bone survey. The PDT candidate patients who agreed to take part in the study had to sign informed consent. Photo sensitizer (Foscan<sup>R</sup>) 0,15mg/kgBW was injected to NPC patients and followed by 20 joule/cm<sup>2</sup>, 642 wave length and 100 watts/cm<sup>2</sup> irradians non thermal laser illumination 96 hours after injection. The PDT result was confirmed with biopsy, CT scan, upper abdominal USG, thoracic photograph, and bone survey 12 weeks after the treatment was given. Follow up was done every 3 months in the first year, and was continued every 6 months in the second year, and was followed once a year. The ethical clearance was approved by Gadjahmada ethical commision, and all statistical analyses were done with SPSS version 17.0.

## RESULTS

The sample of study were collected from January 2005 to December 2010. Thirty three NPC patients post PDT, but only 20 NPC patients were met the inclusion and exclusion criteria, 13 patients were excluded due to primary tumor more than 1 cm<sup>3</sup> in size, consisting of 10 males and 10 females with an age range of 22-73 years

old, the mean age was 46 year-old, and follow up range was 17-86 months. The sample characteristics were shown in Table 1.

Table 1. Sample characteristics

	PDT	%
Age		
10 - 19 yrs	-	-
20 - 29 yrs	3	15%
30 - 39 yrs	2	10%
40 - 49 yrs	3	15%
50 - 59 yrs	9	45%
60 - 69 yrs	2	10%
70 - 79 yrs	1	5%
Stage		
III	12	60%
IVA	3	15%
IVB	5	25%
Gender		
Male	10	50%
Female	10	50%
Histopathology		
WHO II	5	25%
WHO III	15	75%

The 5-year-overall survival rate of local-partial remission of NPC with additional PDT post standard therapy was 50% (Figure 1). There was no significant difference between 5-year-over all survival rate of the sample of >46 year-old and ≤46 year-old with p=0.457 and Log rank 0.554 (Figure 2).

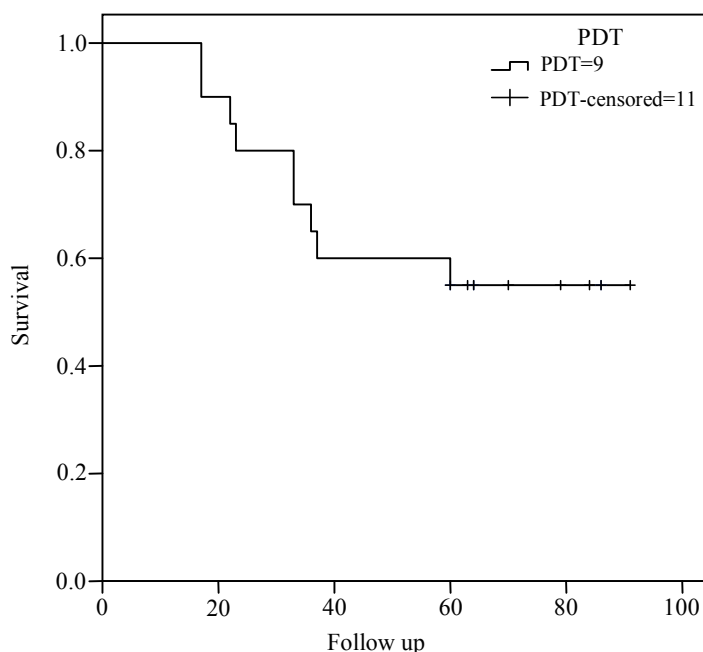


Figure 1. Five-years overall survival rate

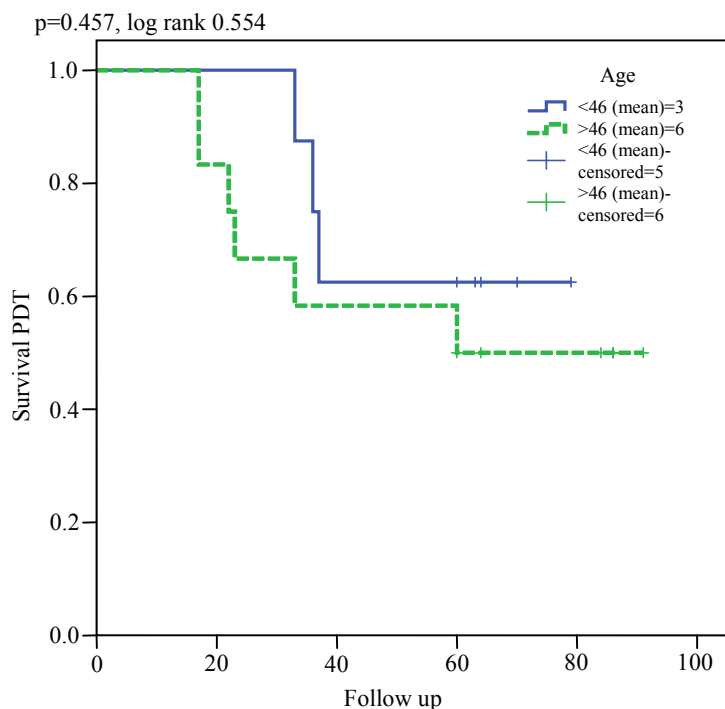


Figure 2. The difference of 5 year-overall survival rate between >46 & ≤46 years old

**DISCUSSION**

Many researchers reported that the therapeutic success rate of NPC in each domestic and international centre or hospitals varied.<sup>1,6,8</sup> This conditions due to the equipment for established NPC diagnose and treatment scheme are not same. The magnetic resonance imaging (MRI) examination for NPC staging is one of the significant prognostic factors beside radiotherapy schedule and chemotherapy scheme.<sup>13</sup> Unfortunately not all of hospitals in Indonesia has not been completed yet with MRI instrument, and the radiotherapy is not on scheduled (too long waiting time) due to the limited radiotherapy equipment. The 3-years-overall survival rate in head and neck malignancy treated with chemotherapy plus radiotherapy was significantly different from that in head and neck malignancy treated with surgery plus radiotherapy ( $p=0.02$ ).<sup>14</sup>

Many overall survival rates of NPC studies have been published. According to Ma, *et al.* study in 5 years survival rate between NPC completed with MRI examination, treated with on time scheduled radiotherapy combined with chemotherapy and NPC treated with radiotherapy only, described that there were no significant differences between the 5-year-overall survival rate in NPC treated with radiotherapy combined with chemotherapy, and NPC treated radiotherapy only. The rate was 63% and 56% ( $p>0.05$ ).<sup>2</sup> A retrospective study by Khademi, *et al.* confirmed that 2-years-overall survival rate of all stages of NPC post therapy was only 35%. The incidence of local relapse

and distant metastasis in the advanced disease is remarkable and the patients with T<sub>2-4</sub>N<sub>2-3</sub> had worse prognosis than those with T<sub>1-2</sub>N<sub>0</sub>. It can be assumed that the different therapeutic success rates might be due to the different diagnostic and therapy scheme or dose and radio-diagnostic and/or radio-therapy equipment in every centre or hospitals. Consequently, different strategies may be needed to improve the treatment outcome.<sup>6</sup>

The research of Wideman, *et al.* reported that 6 NPC patients with T<sub>1-2</sub> post chemo radiation without lymphnode and distance metastasis had complete respons after PDT, and 1 patient died 12 months after PDT cause of unrelated cause.<sup>15</sup>

Hariwiyanto (2010) in earlier research showing that in Sardjito Hospital, the 5-years-overall survival rate in total remission of 28 patients NPC post therapy was 42% and significantly dropped to 20% in partial loco-regional remission of NPC post therapy without additional therapy ( $p<0.05$ ).<sup>16</sup> The result of this study in accordance to our earlier research, showing that the 5 years survival rate of NPC partial remission plus PDT as additional therapy was 50%, significantly better than NPC partial remission without additional treatment (20%).<sup>16</sup>

Another result of the study was no difference of 5-years-overall survival rate between age >46 year-old and ≤46 year-old ( $p=0.457$ ; log rank=0.554). The result was consistent with that of Liu, *et al.* study, reporting there was no difference in 5-year-overall survival rate

between NPC patients <50 year-old and those  $\geq$ 50 year-old ( $p=0.069$ ).<sup>1</sup> Our previous study also discovered that there was no significant different therapy response between NPC >40 and year-old and NPC  $\leq$ 40 year-old ( $p>0.05$ ).<sup>17</sup> The NPC tumor stage was not analysed in this research due to the sample size was not homogen and limited between each stage.

## CONCLUSION

Since the frequent of partial remission is still high and treatment option for recurrent and persistent NPC are limited, the survival rate poor and the complications is severe, alternative treatment modalities is needed with more efficacy and less morbidity. Photodynamic therapy as an additional treatment for small local-partial remission (tumor less than 1 cm) in NPC post treatment is promising as an alternative therapy strategy to improve the treatment outcome and survival rate.

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