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Xerostomia Severity and Quality of Life after Nasopharyngeal Cancer Radiotherapy: Intensity Modulated vs Two-dimensional Radiation Therapy in Indonesia

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Abstract

Background: Two-dimensional technique (2DRT) is most commonly used in Indonesia. This technique causes severe late toxicity particularly in nasopharyngeal cancer (NPC). Radiation techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Three-Dimensional Conformal Radiation Therapy (3DCRT) provide larger doses at the site of NPC while preserving normal tissue. This study aims to compare late side effects and quality of life (QoL) between IMRT and 2DRT groups.

Methods: This was a cross-sectional study with consecutive sampling. Salivae samples were collected at least 6 months after last radiation date. Xerostomia severity were determined by measuring whole saliva flow rate which then categorized based on Common Terminology Criteria for Adverse Events (CTCAE). European Organization for Research and Treatment of Cancer (EORTC) core questionnaire and EORTC head and neck module (QLQ-H&N35) wereused to assess QoL.

Results: The IMRT group had higher saliva flow rate than 2DRT group (1,085 ±0,409 vs 0,188 ± 0,219 stimulated, 0,500±0,254 vs 0,196 ±0,156 unstimulated, $p<0.001$). According to CTCAE, IMRT group experienced less grades 2 and 3 of xerostomia compared to 2DRT group ($p<0.05$). Moderate correlation between recovery time and saliva flow rate ($p<0.05$) was found in IMRT group at least 6 months after last radiation date. QLO-C30 scores were higher in IMRT group than those in 2DRT group, particularly in global health status, physical functioning, emotional functioning, pain and insomnia ($p<0.05$). IMRT group scored better in several QLQ-H&N35 subscales namely head and neck pain, swallowing, speech problems, trouble with social eating, trouble with social contact, dry mouth ($p<0.05$) and sticky saliva ($p<0.001$).

Conclusions: IMRT was significantly superior to 2DRT in preserving and sparing the salivary gland especially parotid and improving quality of life .Thus, we recommend to treat NPC cases in Indonesia with IMRT to reduce toxicity of the treatment and improve quality of life, as it commonly affects people at productive age.

Keywords: Prostate cancer, PSA, EBRT, radiation dose

Background

The mainstay management of nasopharyngeal cancer is surgery and radiotherapy. However, the location of the nasopharyngeal cancer, which is difficult to achieve and obtain sufficient incisions, complicates surgical procedures for this cancer. Therefore, radiotherapy is the first choice because it is able to produce good results and is able to reach difficult areas.[1]

Nowadays, nasopharyngeal cancer therapy provides better survival rates and local control due to technological developments and numerous studies on nasopharyngeal cancer. The use of chemotherapy combined with radiation has been shown to increase the survival

of patients, especially at advanced stages. Moreover, the development of diagnostic technology and improved radiation techniques play a role in increasing the success of nasopharyngeal cancer therapy. Radiation techniques such as IMRT (intensity modulated radiation therapy) or 3DCRT (three-dimensional conformal) or a combination with brachytherapy can provide larger doses at the location of nasopharyngeal tumors but reduce toxic side effects on normal tissue.

Radiation in nasopharyngeal cancer in Indonesia is currently the main choice of therapeutic modality. The use of radiation techniques in most patients in Indonesia is a conventional type using two-dimensional techniques. This two-dimensional (2D) technique causes severe late side effects of advanced toxicity. The most common toxicity caused by radiation is xerostomia.

IMRT techniques that have been running since 2009 provide new hope in improving the quality of therapy. The IMRT technique can limit the radiation dose received by critical organs including the parotid gland so that this technique can improve xerostomia specifically and the quality of life of patients in general. This study aims to compare the further side effects caused by the IMRT and 3DCRT techniques, especially xerostomia degrees and quality of life scores.

Materials and Methods

This study was a cross-sectional analysis to compare xerostomia severity and quality of life of NPC patients treated with 2D techniques with those using the IMRT technique at Department of Radiation Oncology, Dr. Cipto Mangunkusumo Hospital, Indonesia from August 2012 until December 2012.

Results

A total of 40 eligible patients were divided into two groups.Subjects' age ranged from 17 to 60 years with a mean age of 43.7 years in the 2D group, and 18 to 68 years with an average age of 48.3 years in the IMRT group. Most of the patients are male. The technique being used were equivalent in this study. The median of recovery time was 14,86.

Measurement of the flow of saliva was divided into stimulated and not stimulated. At the not stimulated salivary flow rate using an independent sample T-test where 2D techniques have a mean of 0.196 (SD 0.156) (95% CI 0.12; 0.61) ml / minute with a median value of 0.20 ml / minute while the IMRT technique has a mean 0.5 (SD 0.254) (CI95% 0.38; 0.61) ml / minute with a median value of 0.50 ml / minute. at stimulated salivary flow rate, 2D technique has a mean of 0.188 (SD 0.219) (CI95% 0.08; 0.29) ml / minute with a mean value of 0.10 ml / minute while the IMRT technique has an average value of 1.085 (SD 0.409) (CI95% 0.89; 1.27) ml / minute with a median value of 1.00 ml / minute.

Table 1. Subject Characteristics

	Mean ± SD or Median (min-max) or N (percentage)
Age	**45.97 ± 13.1**
Gender	
Men	**26 (65%)**
Women	**14 (35%)**
Staging	
1	**1 (2,5%)**
2	**14 (35%)**
3	**15 (37,5%)**
4	**10 (25%)**
Radiation Technique	
2D	**20 (50%)**
IMRT	**20 (50%)**
Recovery time	**14.86(5.78-39.72)**

Table 2. Stimulated and unstimulated salivary flow rate difference in 2D and IMRT group

	2D (n= 20)	IMRT (n=20)	P value
Stimulated salivary flow rate, ml/s (mean± SD)	**0,188 ± 0,219**	**1,085 ± 0,409**	**<0,001[a]**
Unstimulated salivary flow rate, ml/s (mean± SD)	**0,196 ± 0,156**	**0,500 ± 0,254**	**<0,001[b]**

a Mann-Whitney test, b independent T test

Table 3. Proportion of xerostomia severity (Grade 1 vs Grade 2 and 3) based on CTCAE category in 2D and IMRT group

Radiation Technique	CTCAE Category		Total	P value
	Grade 1	Grade 2+3		
2D	**7**	**13**	**20**	**<0,05[a]**
IMRT	**16**	**4**	**20**	
Total	**23**	**17**	**40**	

a Chi-square test

Table 4. Proportion of xerostomia severity (Grade 1+2 vs Grade 3) based on CTCAE category in 2D and IMRT group

Radiation Technique	CTCAE Category		To-tal	p value
	Grade 1+2	Grade 3		
2D	**13**	**7**	**20**	**<0,05[b]**
IMRT	**19**	**1**	**20**	
Total	**32**	**8**	**40**	

b Fisher's exact test

The comparison of salivary flow rates not stimulated between radiation techniques if converted to the degree of the Common Terminology Criteria for Adverse Events (CTCAE version 3).

The results of the calculation of salivary flow rate statistics based on the CTCAE category. The degree of xerostomia using 2D radiation techniques there are 7 cases of grade 1, 6 cases of grade 2 and 7 cases of grade 3 while those using the IMRT technique have 16 cases of grade 1, 3 cases of grade 2 and 1 case of grade 3.

Correlation between recovery time and saliva flow rate

The relationship between recovery time and salivary flow rate was divided into two groups, namely 2D and IMRT techniques. In 2D techniques, the correlation of recovery time with salivary flow rate not stimulated using Pearson correlation test was r = 0.108 and p = 0.652. On the correlation of recovery time with stimulated saliva flow rate using the spearman correlation test was r = 0.272 and p = 0.246 (**Figure 1**). In the IMRT technique, the correlation of recovery time with the salivary flow rate was not stimulated using the Spearman correlation test obtained r = 0.555 and p = 0.011. The correlation of recovery time with stimulated saliva flow rate using the spearman correlation test with r = 0.517 and p = 0.02 (**Figure 2**).

Correlation between salivary flow rate and average dose received by the parotid gland (IMRT)

The results of the correlation test between the average dose of the parotid gland (Gy) and the salivary flow rate. the correlation test was divided into two, stimulated saliva flow rates and not stimulated in subjects who received therapy with the IMRT technique. At parotid, average doses with not stimulated salivary flow rate using Pearson bivariate correlation test obtained r = -0.521 and p = 0.018. At parotid average doses with stimulated saliva flow rate using Pearson bivariate correlation test, r = -0.458 and p = 0.042 (**Figure 3**)

The results of the EORTC questionnaire data

The results of the EORTC questionnaire data were divided into 2 groups, namely the quality of life questionnaire in general with the QLQ-C30 and a more specific questionnaire asking about the area of the neck head with the QLQ-H & N35 (**Table 5**). In processing the QLQ-H & N35 questionnaire data using the Mann Whitney test there were significant differences in pain (HNPA) , swallowing (HNSW) , speech problems (HNSP), trouble with social eating (HNSO) , trouble with social contact (HNSC) , dry mouth (HNDR).

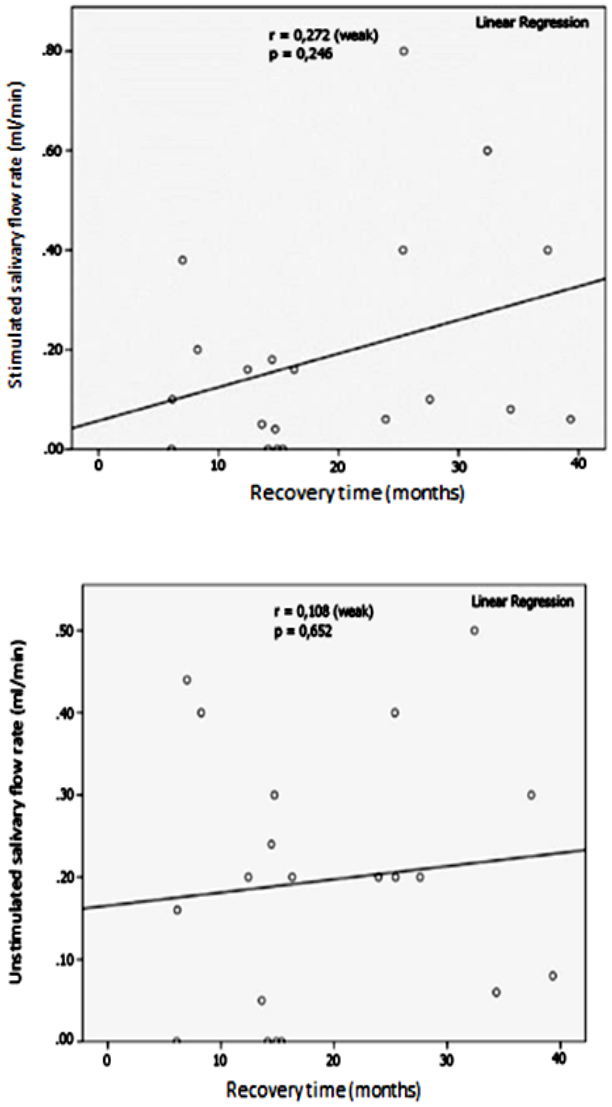
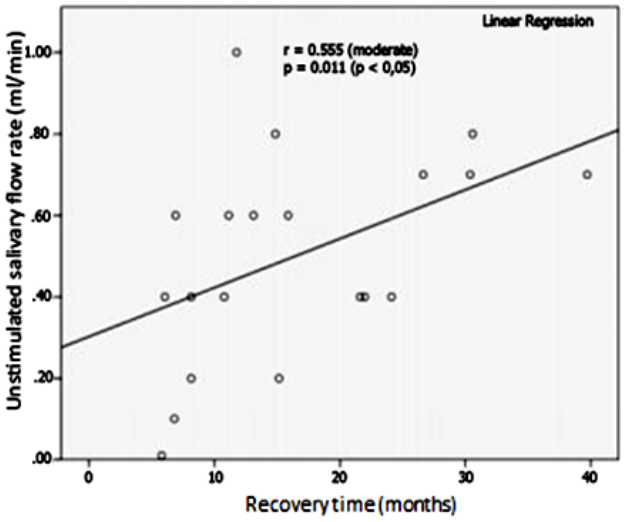


Figure 1. Correlation between salivary flow rate (stimulated vs unstimulated) and recovery time in 2D group



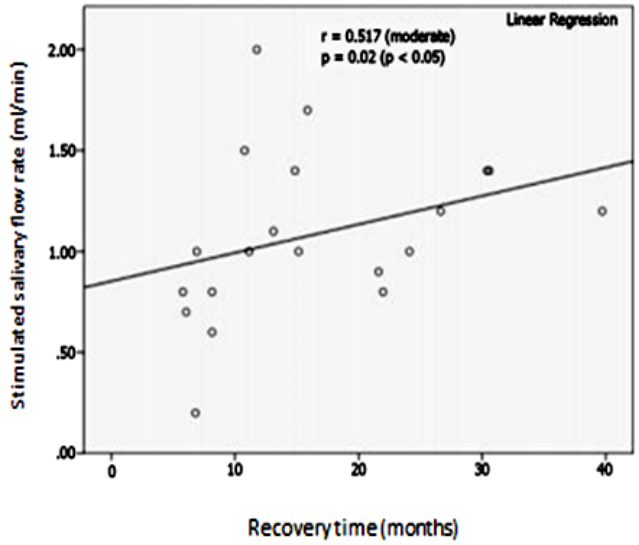


Figure 2. Correlation between salivary flow rate (stimulated vs unstimulated) and recovery time in IMRT group

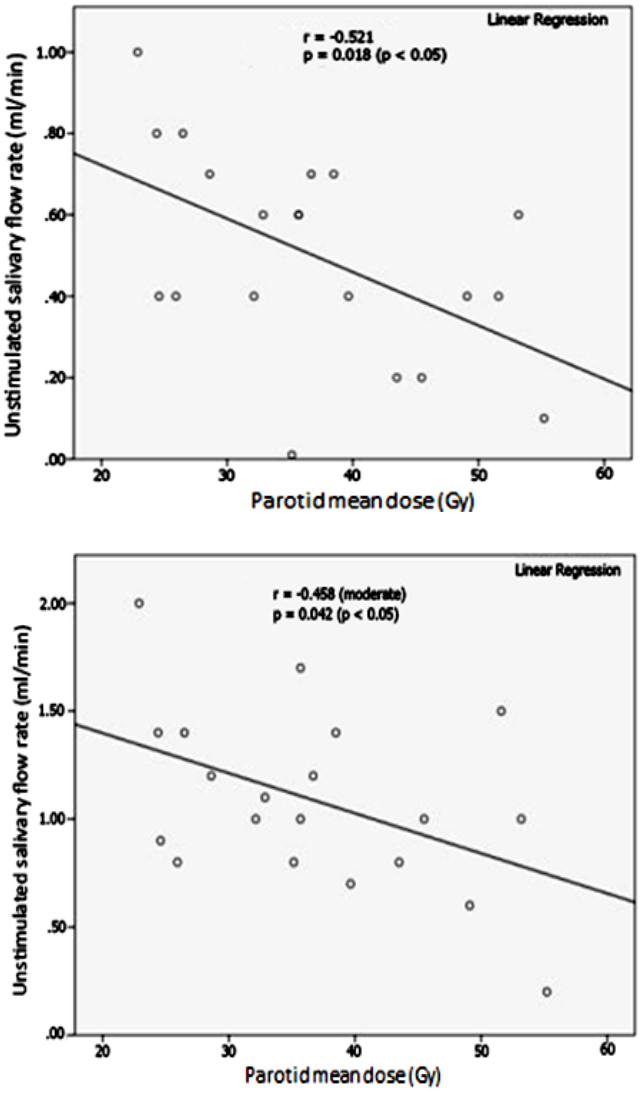


Figure 3. Correlation between salivary flow rate (stimulated vs unstimulated) and parotid mean dose in IMRT group

Table 4. QLQ-C30 questionnaire score difference between 2D and IMRT group

Indicator	2D (median)	IMRT (median)	p value‡
Global Health Status /QoL (QL2)	66,6	87,5	0.008*
Physical functioning (PF2)	80	96,6	0.006*
Role functioning (RF2)	83,3	100	0.070
Emotional Functioning (EF)	75	95,8	0.001*
Cognitive Functioning (CF)	83,3	100	0.090
Social Functioning (SF)	83,3	91,6	0.490
Fatigue (FA)	22,2	22,2	0.210
Nausea and Vomiting (NV)	0	0	0.522
Pain (PA)	16,6	0	0.044*
Dyspnoea (DY)	0	0	0.190
Insomnia (SL)	16,6	0	0.038*
Appetite Loss (AP)	16,6	0	0.121
Constipation (CO)	0	0	0.681
Diarrhoea (DI)	0	0	0.971
Financial difficulties (FI)	66,6	0	0.074

‡: Mann-Whitney test, *: statistically significant

Table 5. QLQ-H&N35 questionnaire score difference between 2D and IMRT group

Indicator	2D (median, min-max)	IMRT (median, min-max)	p value‡
Pain (HNPA)	8,3	0	0,023*
Swallowing (HNSW)	25	12,5	0,031*
Senses problems (HNSE)	16,6	8,3	0,097
Speech problems (HNSP)	22,2	0	0,047*
Trouble with social eating (HNSO)	33,3	8,3	0,016*
Trouble with social contact (HNSC)	13,3	0	0,022*
Less Sexuality (HNSX)	16,6	8,3	0,483
Teeth (HNTE)	33,3	33,3	0,697
Opening mouth (HNOM)	33,3	0	0,064
Dry Mouth (HNDR)	66,6	50	0,013*
Sticky Saliva (HNSS)	66,6	33,3	<0,001*
Coughing (HNCO)	16,6	0	0,094
Felt ill (HNFI)	33,3	0	0,117

ǂ: Mann-Whitney test, *: statistically significant

Discussion

Based on previous research by Lee et al., in the management of nasopharyngeal cancer, the IMRT technique has severe mucositis side effects. It happened because the accumulation of doses was quite high in the oral mucosa.[2] Xerostomia is the main symptom of late side effects in nasopharyngeal cancer. the salivary flow rate decreased after the salivary gland received a dose of 10-15 Gy. Saliva production continues to decline to doses of 20-40 Gy, and above 40 Gy decreases to more than 75% of production.[3]

The IMRT group made the higher saliva flow rate than 2DRT group ($p < 0.001$) both at the stimulated saliva flow rate and not stimulated. This indicates that the salivary gland still has better function after radiation with the IMRT technique than 2D techniques. In the comparison of stimulated and not stimulated salivary flow rates in the 2D group, there was no significant difference ($p = 0.23$) whereas in the IMRT group there were significant differences ($p < 0.001$) where when the parotid gland was stimulated by food, more saliva would be produced than the saliva flow rate is not stimulated.

If categorized into CTCAE criteria the IMRT group achieve better degree of xerostomia than 2DRT group ($p<0.05$). Similar findings were reported by a meta-analysis study by Gupta et al. IMRT significantly reduced the risk of ≥grade 2 late xerostomia (RR = 0.44, 95%CI = 0.34-0.57; p = 0.00001) compared to non-IMRT techniques at all time-points.[4] The use of the IMRT technique is more experienced in lower degrees of xerostomia (degree 1), while the use of 2D has a higher degree of xerostomia (second and third degree). This means that the IMRT technique did not damage the salivary gland too much and the salivary gland can still work better than 2D techniques in 2D group, there was a weak correlation between recovery time and saliva flow rate. The longer the recovery time, the higher the saliva flow rate. But this statistic does not have a significant relationship. based on this study, it was found that the salivary flow rate cannot recover over time. too large doses received by the salivary gland cause this to happen. In 2D techniques opposing laterally, the parotid gland can be exposed to a dose of 60-70 Gy. whereas in the literature it is said that the maximum dose of the parotid gland to irreversible is 60 Gy.[5] Whereas in IMRT group, there was a moderate correlation between recovery time and saliva flow rate ($p < 0.05$) where the longer the recovery time, the higher the salivary flow rate both at the stimulated salivary flow rate and not stimulated. This proves that IMRT patients after salivary gland radiation therapy can recover over time.

From the QLO-C30 questionnaire score, the IMRT group prove to be better than 2DRT group in categories: Global health status, physical functioning, Emotional functioning, pain and insomnia ($p<0.05$). From the head and neck module questionnaire (QLQ-H&N35), IMRT group also prove to be better in categories : head and neck pain. Swallowing, speech

problems, trouble with social eating, trouble with social contact, dry mouth ($p<0.05$), & sticky saliva ($p<0.001$). Fatima et al conducted a study comparing QoL between conventional radiotherapy arm and IMRT arm. The conventional arm had a mean score of 8.5 ± 2.47 (±2sd) whereas the IMRT arm had a mean score of 4.8 ± 3.8 with significant difference (p 0.003).[6] A study done by Jabbari et al also showed better xerostomia related QoL questionnaire score in IMRT arm compared to standard RT arm.[7] Overall the use of the IMRT technique has been shown to reduce the side effects of xerostomia and provide a better quality of life. xerostomia in the IMRT group can also improve over time. however, there is a lack in the EORTC questionnaire in the form of no measurement criteria for hearing function. reduced hearing function is one of the most side effects besides xerostomia and soft tissue fibrosis.[8] So far, xerostomia is believed to be the main factor causing the decline in the quality of life of patients, but the direct causal relationship between these two things cannot be ascertained. The use of the IMRT technique in nasopharyngeal cancer not only reduces xerostomia complaints but also in other organs in the head and neck region which ultimately improves overall quality of life.[9]

Conclusions

Nasopharyngeal cancer radiation techniques with IMRT have been shown to relieve severe side effects compared to 2DRT. IMRT was significantly superior to 2DRT in preserving and sparing the salivary gland especially parotid. Less side effects compared to 2DRT also affect the quality of life of patients both medically and in general. This study recommends IMRT as the technique to treat NPC patients in Indonesia in order to reduce toxicity and improve quality of life.

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