JMU
Jurnal Medika Udayana

ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 13 NO.02, FEBRUARI, 2024

DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

Accredited SINTA 3

Received: 2023-08-05 Revision: 2023-11-28 Accepted: 02-01-2024

ACUTE SIDE EFFECTS AND QUALITY OF LIFE IN HEAD AND NECK CANCER PATIENTS WHO UNDERWENT RADIOTHERAPY IN BALI, INDONESIA

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ABSTRACT

Background: Radiotherapy is a therapeutic modality for head and neck cancer which kills cancer cells with radiation waves. In addition to damaging cancer cells, radiotherapy also damages healthy body cells around the target tissue. Damage to healthy body cells causes a side effect of toxicity from radiotherapy. Side effects of radiotherapy cause a decrease in quality of life in patients undergoing radiotherapy. As technology advances, there are many types of teletherapy tools being developed.
Purpose: The aim of this study is to compare the acute side effects and quality of life of the patients who underwent radiotherapy with different equipment; Cobalt-60 and LINAC (Linear Accelerator).
Patients and Methods: This was an analytic observational study, performed on head and neck cancer patients who underwent radiotherapy between January 2020 and July 2022 at radiotherapy department, RSUP Prof. Dr. IGNG Ngoerah, Bali. We measure patient's quality of life with EORTC QLQ-C30 questionnaire and acute side effects with RTOG grading. The average value and comparison of both teletherapy devices were assessed using cross tabulation and analyzed with Statistical Package for Social Science (SPSS) version 26.0.
Result: This study admitted 52 patients (35 LINAC and 17 Cobalt-60) who met inclusion and exclusion criteria. Most of the participants in this study were 49-60 years old (50%), male (63.7%), the main location of cancer was in the nasopharynx (84.6%), and the prognosis stage was 4A (57.7%). Comparison between both groups showed p value >0.05 on acute side effects and quality of life. Most patients experienced Grade 1 RTOG side effects on skin, salivary glands, pharynx and esophagus, and larynx. The LINAC group had a higher percentage (94.3%) of "good" general condition compared to the Cobalt 60 group (76.5%). The lowest function scale based on EORTC QLQ-C30 was role function (51.9 ± 31.8), and the highest score of symptoms scale was fatigue (50.0 ± 31.2).
Conclusion: There are no significant differences in acute side effects and quality of life of patients who underwent radiotherapy with LINAC and Cobalt-60 teletherapy. However, the LINAC group has a larger percentage of "good" general condition compared to Cobalt-60 group.
Keywords: Cobalt-60., LINAC., Acute Side Effect., Quality of Life., Radiotherapy.

INTRODUCTION

Head and neck cancer can originate from nasopharynx, thyroid, lips and oral cavity, larynx, salivary glands, oropharynx, esophagus and hypopharynx. Head and neck cancer contributed 42,814 new cancer cases or 12.27% of all new cancer cases in Indonesia recorded in The Global Cancer Observatory in 2018. The 6th cause of death in Indonesia. [1] Head and neck cancer is more common in men than women and people aged between 50 and early 60 years in Asian countries. [2]

Radiotherapy or radiation therapy is a cancer treatment that uses high levels of radiation to kill cancer cells and reduce the size of tumors. On the other hand, radiotherapy not only kills cancer cells, but also healthy cells around them. [3] Radiotherapy with Cobalt 60 uses gamma rays to treat cancer. Starting in the 1950s, cobalt 60 was used as an external therapy to kill cancer cells. Cobalt 60 produces a stable dichromatic emission of 1.25 mega volts and has a half-life of 5.3 years so the radiation source must be replaced periodically. However Cobalt 60 is starting to be replaced by Linear Accelerator (LINAC).[4] Linear Accelerator is a type of machine that accelerates subatomic particles or ions by exposing them to electrical potential in parallel with a straight beam. Various types of particles that can be accelerated according to the engine are protons, electrons and ions. [5]

LINAC offers precise and versatile treatment with cost advantages but requires a higher initial investment and frequent maintenance. Cobalt, on the other hand, has a longer-lasting radiation source but is less versatile. The choice depends on budget and facility resources.[6]

Therapy with radiation is strong enough to injure surrounding normal tissue, leaving behind cell damage that triggers a response from the immune system, as well as activating

a series of chemical and mechanical events within the cells, causing side effects. [7]

Side effects of radiotherapy can cause acute and chronic effects. In the late 1970s, further research began to be conducted to share perceptions of the toxicity assessment of radiotherapy use by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). [8]In head and neck cancer radiotherapy, acute side effects focus on toxicity in skin tissue, salivary glands, pharynx, esophagus, and larynx.[9]While the chronic side effects include salivary loss, osteoradionecrosis, dental issues, skin changes, and chronic sinusitis.[10]In this study, the authors compared the side effects of radiation that occurred in head and neck cancer patients who received radiation on a Cobalt-60 machine with patients who received radiation on a Linear Accelerator (LINAC) machine.

MATERIALS AND METHODS

This is an observational case-control study between January 2020 and July 2022, involving 52 patients diagnosed with head and neck cancer who underwent radiotherapy with Cobalt 60 and LINAC machines with a total dose of 63-70 Gy (divided into 33-35 fractions). Data were obtained from RSUP Prof. Dr. IGNG Ngoerah medical record. Inclusion criteria encompassed diagnosis through radiological and anatomical pathology, while exclusion criteria involved non-completion of prescribed therapy and uncooperativeness. The study used total sampling due to a population size of less than 100. Primary data was gathered through patient questionnaires, while secondary data came from specialists' assessments. The analysis, conducted with SPSS Version 26.0.

This research was approved by the Ethics Commission of the Faculty of Medicine, Udayana University, Bali (No.1733/UN14.2.2.VII.14/LT/2022). Thirty-five and seventeen patients were divided into LINAC group and Cobalt-60 group, respectively. Unequal sample numbers between groups were due to total sampling method used. All patients were provided with complete information regarding the study and *informed consent* was obtained from each patient. Acute side effects on the skin, salivary glands, pharynx and esophagus, and larynx were measured using the *Radiation Therapy Oncology Group* (RTOG) scoring system. The assessment includes grade 0 to grade 4, where grade 0 indicates no toxicity or no change , grade 1 indicates mild changes (dermatitis/mucositis/dysphagia), grade II indicates moderate and symptomatic (moist desquamation/patchy mucositis/sticky saliva and dysphagia), grade III indicates severe changes (desquamation/confluent mucositis/dryness and dysphagia), grade IV indicates excruciating and debilitating changes (ulcer, bleeding, necrosis, complete obstruction or fistula). Quality of life was quantified with the Indonesian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). The questionnaire is completed with patient self-assessment responses. The questionnaire consists of 30 items (physical, role, cognitive, emotional and social functioning), a Global Health Status (GHS), three symptom scales and six single item scales. All responses were converted to a 0–100 scale. Scores were calculated based on the EORTC QLQ-C30 scoring manual. Higher scores for the functional scale and for the global QOL scale indicate better QOL. For symptom-oriented scales and items, higher scores correspond to higher levels of distressing symptoms.Acute adverse events were categorized by RTOG from 0 to 4. In the general health category and on the functional scale, "good" status was assigned an EORTC score of ≥ 50 points. In the symptom category, "good" status is given when an EORTC score is <50 points. Chi Square tests were used to calculate mean scores and p values for the QOL scales. The significance of correlation between groups was determined based on a p value <0.05 which was considered statistically significant.

RESULTS

The number of patients who met the inclusion and exclusion criteria was 52 people, consisting of 17 patients treated with the Cobalt-60 teletherapy device and 35 patients treated with the LINAC teletherapy device.The majority of patients treated with the LINAC teletherapy device were 35 people (63.7%), while the number of patients treated with the Cobalt-60 teletherapy device was 17 people (32.7%). The largest gender in this study was male, totaling 37 people (71.2%). The average age of patients in this study was 52.9 years. Patients in the 49-60 year age group were 26 people (50%) which was the largest. There were 14 (27%) patients aged 37-48 years, 10 (19.2%) patients aged 61-72 years, and 2 (3.8%) patients aged 24-36 years. The most common tumor location found in patients was the nasopharynx, namely 44 people (84.6%). Tumors in the pharynx were found in 3 people (5.8%). Other tumors were located in the oral cavity, sinonasal cavity, salivary glands, thyroid and neck (9.6%). The most prognostic stage diagnosis was stage 4A, namely 30 people (57.7%), followed by stage 4B with 8 people (15.4%), stage 4C with 7 people (13.5%), stage 4C with 6 people (11.5%). stage 3, and 1 person (1.9%) in stage 1.

Table 1. Patient Characteristics

Parameter		Frequency	Proportion
Teletherapy	Cobalt-60	17	32.7
	LINAC	35	63.7
Gender _	Man	37	71.2
	Woman	15	28.8
Age (Mean ± SD: 52.9 ± 9.7)	24–36	2	3.8
	37 –48	1 4	27, 0
	49–60	26	50, 0
	61–72	1 0	19, 2
Tumor Location	Nasopharynx	44	84.6
	Larynx _	3	5.8
	Oral cavity	1	1.9
	Sinonasal cavity	1	1.9
	Gland saliva	1	1.9
	Thyroid	1	1.9
	Neck (DSFP)	1	1.9
Prognosis Stage (AJCC 8th)	1	1	1.9
	3	6	11.5
	4A	30	57.7
	4B	8	15.4
	4C	7	13.5

In this study, the majority of patients experienced Grade 1 acute skin adverse events; Cobalt group 60 (88.2%), LINAC group (74.3%). In the salivary gland side effect parameters, it was found that the Cobalt 60 group experienced more severe side effects, Grade 2 (23.5%). In the Cobalt 60 group, a greater proportion of acute pharyngeal and esophageal adverse events were found in grade 1 (47%) and grade 2 (41.2%), similar results were observed in the LINAC group; most patients experienced grade 1 (57.1%) followed by grade 2 (34.3%). Two of the thirty-five patients in the LINAC group experienced grade 4 pharyngeal and esophageal side effects. Most patients in both groups experienced grade 1 laryngeal side effects. Based on statistical tests, there was no significant difference in acute side effects ($p<0.05$) between patients using Cobalt-60 and LINAC teletherapy devices. However, it was found that all patients participating in the study had acute side effects on the skin, salivary glands, pharynx and esophagus, as well as the larynx.

Table 2 . Comparison effect side acute on both group

Category	Cobalt-60 (Grade) *n* =17					LINAC (Grades) *n* =35					p value
	0	1	2	3	4	0	1	2	3	4	
Skin [*n*] (%)	0	15 (88.2%)	2 (11.8%)	0	0	1 (2.9%)	26 (74.3%)	8 (22.8%)	0	0	0.472
Gland Saliva [*n*] (%)	0	13 (76.5%)	4 (23.5%)	0	0	0	29 (82.9%)	6 (17.1%)	0	0	0.584
Pharynx and Esophagus [*n*] (%)	0	8 (47.0%)	7 (41.2%)	2 (11.8%)	0	1 (2.9%)	20 (57.1%)	12 (34.3%)	0	2 (5.7%)	0.204
Larynx [*n*] (%)	2 (11.8%)	11 (64.6%)	2 (11.8%)	2 (11.8%)	0	8 (22.9%)	11 (31.4%)	6 (17.1%)	8 (22.9%)	2 (5.7%)	0.227

Note: Assessment of acute side effects according to the Radiation Therapy Oncology Group (RTOG) criteria, morbidity levels (e.g. Grade 0 –no change, grade IV – excruciating changes) is described in the 'Materials and methods' section. This data is objective – with clinical judgment.

Most of the patients' global health status was generally in "good" condition. In the functional scale category, the physical, emotional and emotional function variables are mostly in "good" condition. However, for role function, almost half of the patients treated with LINAC teletherapy devices were in “poor” condition. The role function has the highest number of patients in “bad” condition. Cognitive and emotional functions in both groups were all in "good" condition.

In the symptom scale category, fatigue was the symptom most frequently experienced by patients in both groups. Complaints of shortness of breath and diarrhea were not found in patients treated with Cobalt-60. Financial difficulties were not found in either group. Based on statistical tests, there was no significant difference in quality of life ($p>0.05$) between patients who used Cobalt-60 and LINAC teletherapy.

Table 3 . Comparison quality live on both group

Parameter	EORTC QLQ C30 Mean Score ± SD	Cobalt-60 *n* =17		LINAC *n* =35		p value
		Good	Bad	Good	Bad	
Global Health Status [*n*](%)	65.5 ± 18.1	13 (76.5%)	4 (23.5%)	33 (94.3%)	2 (5.7%)	0.06
Functional Scale						
Physical function [*n*](%)	71.9 ± 25.1	13 (76.5%)	4 (23.5%)	30 (85.7%)	5 (14.3%)	0.40
Role Function [*n*](%)	51.9 ± 31.8	10 (58.8%)	7 (41.2%)	18 (51.4%)	17 (48.6%)	0.61
Emotional Function [*n*](%)	81.9 ± 20.1	16 (94.1%)	1 (5.9%)	33 (94.3%)	2 (5.7%)	0.98
Cognitive function [*n*](%)	89.1 ± 15.8	17 (100%)	0 (0%)	35 (100%)	0 (0%)	-
Social function [*n*](%)	85.9 ± 16.6	17 (100%)	0 (0%)	35 (100%)	0 (0%)	-
Symptoms Scale						
Fatigue [*n*](%)	50.0 ± 31.2	4 (23.5%)	13 (76.5%)	4 (11.4%)	31 (88.6%)	0.26
Nauseous or Vomiting [*n*](%)	20.8 ± 30.4	14 (82.4%)	3 (17.6%)	29 (82.9%)	6 (17.1)	0.96
Pain [*n*](%)	36.2 ± 24.2	14 (82.4%)	3 (17.6%))	29 (82.9%)	6 (17.1%)	0.96
Dyspnea [*n*](%)	8.3 ± 19.7	17 (100%)	0 (0%)	33 (94.3%)	2 (5.7%)	0.32
Insomnia [*n*](%)	23.7 ± 30.5	14 (82.4%)	3 (17.6%)	28 (80.0%)	7 (20.0%)	0.84
Lost Appetite [*n*](%)	24.4 ± 35.0	15 (88.2%)	2 (11.8%)	26 (74.3%)	9 (25.7%)	0.25
Constipation [*n*](%)	26.3 ± 30.5	13 (76.5%)	4 (23.5%)	26 (74.3%)	9 (25.7%)	0.86
Diarrhea [*n*](%)	4.5±13.2	17 (100%)	0 (0%)	34 (97.1%)	1 (2.9%)	0.48
Difficulty Finance [*n*](%)	0.0±0.0	17 (100%)	0(0%)	35 (100%)	0 (0%)	-
Fatigue [*n*](%)	50.0 ± 31.2	4 (23.5%)	13 (76.5%)	4 (11.4%)	31 (88.6%)	0.26

Note: Assessment of quality of life according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 as described in the 'Materials and methods' section. This data is subjective – reported by the patient.

DISCUSSION

In this study, the majority of participants were men (71.2%) with an average age of 52.9 ± 9.7 years. The primary location of the tumor was found in the nasopharynx (84.6%) and the prognostic stage at diagnosis according to the American Joint Committee on Cancer (AJCC) 8th edition was advanced stage 4A (57.7%), 4B (15.4%) and 4C (13.5%). This finding is in accordance with the theory that men are a population that has a greater risk factor for developing head and neck cancer, where the supporting factors for this cancer are the consumption of cigarettes and alcoholic drinks. The trigger factors for oronasopharyngeal cancer are HPV and EBV infections, the tendency of which continues to increase, causing the prevalence of oronasopharyngeal cancer to exceed the incidence of laryngeal and hypopharyngeal cancer.[11] Regarding the findings of many patients diagnosed with advanced stages in

this study, pathologically, the symptoms of nasopharyngeal cancer tend to be ignored by patients because the main tumor grows in the physiological cavity of the body. Therefore, when symptoms appear, it is known that the tumor has grown quite large or metastasized. [12]

Radiation to the head and neck causes acute side effects affecting the skin, oral mucosa, salivary glands, esophagus, etc., which can hamper therapy and reduce the patient's quality of life. Acute side effects after radiotherapy in this study were measured objectively by RTOG assessment. In this study, we did not find a relationship between the type of teletherapy device used and acute side effects on the skin (p=0.472), salivary glands (p=0.584), pharynx and esophagus (p=0.204), or larynx (p=0.227).

Skin erythema (RTOG grade 1) was experienced by the majority of patients after radiotherapy in this study with Cobalt 60 (88.2%) and LINAC (74.3%). These findings are similar to a study conducted by Chugh et al, where the majority of participants undergoing radiotherapy with LINAC experienced grade 1-2 skin side effects. [13] However, this contradicts the findings of Allal et al, who found that most participants experienced more severe skin side effects (grade 3-4). [14]

Most patients in the Cobalt and LINAC groups had grade 1 salivary gland side effects (76.5% and 82.9%, respectively), in which the oral cavity was slightly drier, and saliva was slightly thicker than normal. Dry mouth (xerostomia) is the most common side effect that occurs after radiation for head and neck cancer. [15] RTOG xerostomia grades 3-4 were statistically directly associated with decreased emotional and social functioning as well as increased fatigue and difficulty sleeping. [16] In this study, no patient had normal saliva production after completing one dose of head and neck radiotherapy. Symptoms of xerostomia can persist for up to 5 years after radiotherapy. [17]

Almost all post-radiotherapy patients complained of pharyngeal and esophageal side effects (100% in the Cobalt group and 97.1% in the (LINAC) group). Swallowing function may be impaired due to several abnormal tissue changes including edema, neuropathy, and fibrosis. We found a low proportion of RTOG grade 3–4 acute adverse events in the pharynx and esophagus (11.8% in the Cobalt group and 5.7% in the LINAC group). A similar study by Van der Laan, suggested an increase in the proportion of swallowing difficulties (dysphagia) over time; in grades 3-4, it increased 6% at week 3 and 26% at week 6 post-radiotherapy. [18] There was a significant relationship between severe xerostomia (grade 3-4) and severe acute and chronic dysphagia (grade 3-4), p=<0.0001. [19]

Progressive laryngeal edema and laryngeal fibrosis can cause voice and swallowing disorders. Voice changes are related to radiation dose to the larynx, pharynx, and oral cavity. More specifically, adverse effects on the larynx (grade ≥ 2) occurred after exposure to 66 Gy to this anatomical structure. [20] In this study, the proportion of patients who received a total radiation dose of 63-70 Gy experienced laryngeal side effects varying from grade 0-3 in the Cobalt 60 group (11.8%, 64.6%, 11.8%, 11.8%), and grades 0-4 in the LINAC group (22.9%, 31.4%, 17.1%, 22.9%, 5.7%).

This study shows that there is no significant relationship between the type of teletherapy device used and the quality of life of head and neck cancer patients after radiotherapy. Although not significant, we found some differences between the two groups of participants. The group that received irradiation with the LINAC device had a “good” general health condition (EORTC score≥50 points) with a higher percentage (94.3%) compared to the Cobalt 60 group (76.5%). The average general health status score for all participants in this study (65.5 ± 18.1) was lower than in previous similar studies. Kao got 67.9 ± 14.8, Hammerlid 73.2 ± 21.3 and Liao 70.9 ± 22.1. [21-23]

Among the five functional aspects, the aspect that is most affected is role function. Role function is the patient's ability to carry out daily activities, hobby activities, and work or profession. [24] In this study, we found that the lowest average EORTC QLQ C30 score was in the patient role function category, namely 51.9 ± 31.8 and there was only a slight difference in the proportion of "good" and "bad" between the two groups. The results of previous research also show that the role function category is the lowest of all functions. [24,25] On the other hand, all participants in this study had “good” functioning in the cognitive (mean 89.1 ± 15.8) and social (mean 85.9 ± 16.6) categories. This stance is contrary to the study conducted by Leung et al. where the role function score is the highest among other functions. [26] However, role function is the first gateway to improve quality of life, as it will improve the other counterparts.[27] The differences of function recovery among different cultural backgrounds are strongly encouraged for further research.

The quality of life of cancer sufferers will decrease after cancer therapy. The factors causing the decline in quality of life are still being debated, one of which is socio-economic factors. The study by Kao et al. did not find a significant association, but a study by Liao et al. found that patients with high socioeconomic status had better functioning effects. [21,22] Janda M et al. observed that high levels of education and marital status were associated with better functioning and quality of life. [28]

The EORTC QLQ C30 symptom scale in this study showed an average score of ≤50. This symptom scale has the lowest score compared to the other two scales. The symptom experienced by the majority of patients was fatigue (mean 50.0 ± 31.2) where the percentage in the "bad" category was lower in the Cobalt 60 group (76.5%) and higher in the LINAC group (77.6 %). Several other studies also found that of all the symptoms listed on the scale, fatigue was the most frequently experienced by patients. [22,28,29]

CONCLUSIONS AND SUGGESTIONS

Despite the development of the LINAC and its ability to replace the Cobalt 60 machine, it remains unproven whether one is significantly more useful than the other. However, it is worth mentioning that patients who received radiotherapy with the LINAC device had a higher proportion of "good" general health conditions, compared with the Cobalt 60 group.

Follow-up studies comparing the patient's condition before, after radiotherapy, and follow-up at 1 year can be carried out to determine the evolution of quality of life and side effects. In addition, further studies to find the relationship between demographic data and radiation dose with quality of life and acute side effects should be carried out to determine factors that can worsen and alleviate the patient's condition.

THANK-YOU NOTE

We would like to express our deepest gratitude to all parties who have played a role in completing this research and publishing this article. We are grateful for the generous participation of the study participants, whose time and cooperation were indispensable in collecting the necessary data. We extend our thanks to the healthcare professionals, nurses, and technicians who provided support in data collection, sample analysis, and patient care. In addition, we thank Prof. Hospital. Dr. IGNG Ngoerah has financially supported this research, enabling scientific investigation and health advancement.

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