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# CLINICOPATHOLOGICAL ANALYSIS OF RHABDOMYOSARCOMA PATIENTS UNDERGONE RADIOTHERAPY IN TWO REFERRAL HOSPITALS IN WEST JAVA

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## ABSTRACT

*Rhabdomyosarcoma (RMS) is a type of malignant soft tissue neoplasm that develops from mesenchymal cells of skeletal muscle origin. This condition comprises multiple subtypes with distinct histologic characteristics. While cases of RMS are uncommon overall, they are more frequently diagnosed in children, although adults can also be affected. Treatment options for RMS include radiotherapy, with the specific therapy and dosage determined according to the IRS Group classification system. This study was conducted by collecting secondary data of RMS patients from the medical records consecutively who had been diagnosed and received radiotherapy. The data resources were from Radiotherapy Department and Anatomical Pathology Department of RSUP Dr. Hasan Sadikin Bandung and RSUD Al-Ihsan Bandung, between 2017 and 2023. A total of 31 patients were documented. The age of patients ranging from 3 to 66 years old (mean=34.6), with each of age group (children, adult, elderly) consists of 10, 10, and 11 patients respectively. Based on histologic subtype, most cases of RMS recorded are embryonal subtype (n=10) followed by alveolar RMS and pleomorphic RMS with 6 patients each. The extremities were the most common location (n=13) followed by the head and neck region (n=10). After radiotherapy, 20 cases were accounted as radiosensitive and 11 cases were radioresistant. Thirty one patients with rhabdomyosarcoma have received radiotherapy at two referral hospitals in Bandung between 2017-2023. The tumors in pediatric and elderly patients were more sensitive to therapy. Pleomorphic RMS were the most sensitive subtype, and the larger a tumor, the more sensitive it can be.*

**KEYWORDS** *Clinicopathological, Rhabdomyosarcoma, Radiotherapy, West Java*



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## INTRODUCTION

Rhabdomyosarcoma (RMS) is a malignant soft tissue neoplasm (sarcoma) originating from skeletal muscle mesenchymal cells. This disease consists of several subtypes with various histologic forms and different etiologies, namely embryonal (ERMS), alveolar (ARMS), pleomorphic RMS, and spindle/sclerosing cell RMS (Lindberg MR, 2019; World Health Organization, 2020). In general, RMS cases are rare. It is estimated that there are 6 cases of RMS in every 1 million population worldwide(Goldblum JR et al., 2020). It is more common in pediatric patients, although it can also occur in adult patients. The incidence of RMS in pediatric patients is 3-4% of all pediatric malignancies, and decreases to 2% in patients over the age of 45. (Goldblum JR et al., 2020; McEvoy MT & et al, 2023) In the United States, the number of RMS cases can reach 500 cases per year. (American Cancer Society, n.d.) However, there is no complete data on these cases in Indonesia. The etiology and risk factors for RMS are still largely under research and depend on the histologic subtype. These differences are thought to influence the incidence of each RMS case. For example, ERMS tends to be more common in pediatric patients, whereas ARMS is more common in adults.

There are certain methods to treat RMS. Surgery through resection is the initial choice in starting treatment (Brunicardi FC, 2019). Systemic therapy with chemotherapy is the next stage which is now routinely carried out in various adequate health facilities (European paediatric Soft tissue sarcoma Study Group (EpSSG), 2012). Meanwhile, radiotherapy is performed after chemotherapy with the aim of local control. Radiotherapy criteria are determined based on the IRS (Intergroup Rhabdomyosarcoma Studies) group which is divided according to the type of resection performed (Raney RB & et al, 2001). IRS Group I is a histopathologically proven complete resection. Group II is resection of the tumor mass until it is not visible macroscopically, but is still detected microscopically. As for group III, there is still visible tumor mass left in-situ. Radiotherapy is given to group II-III tumors, including metastases, and is given to all groups as long as the tumor is ARMS. It is only given if the patient is over 3 years old. Currently there is no sufficient data on the effect of radiotherapy on RMS in Indonesia, especially in West Java Province. The aim of this study is to analyze the clinicopathological features of RMS patients who undergone radiotherapy in two referral hospitals in Bandung, West Java capital.

## RESEARCH METHOD

This is a descriptive study that conducted by collecting data from the medical records of the Department of Radiology Oncology/Radiotherapy of Dr. Hasan Sadikin Hospital Bandung and Al-Ihsan Hospital Bandung, between 2017 and 2023. It revealed a total of 31 patients in which clinical and histopathological data was carried out. The data included are gender, age, tumor size, and response to radiotherapy. Radiotherapy response was assessed based on European Cooperative Group (ECoG) measurement standards according to radiology results and clinical information. While the determination of the histopathology type of RMS was based on the results of routine examination of paraffin blocks (Hematoxylin-Eosin staining) with immunohistochemistry (desmin/ myogenin/myoD1) as complementary.

## RESULT AND DISCUSSION

The study has been carried out descriptively by collecting secondary patient data through medical records which can be seen from table 1 below. It showed that in terms of gender, males outnumbered females by a ratio of 1.4:1. The average age of patients was

34.6 years old, with the youngest patient being 3 years old, and the oldest being 66 years old. Each of age group consists of nearly an equal number of individuals. Pediatric patients (≤18 years) and adults (19-49 years) share similar number of 10 patients. Elderly group (≥50 years) was 11 patients.

Based on histologic subtype, there are 10 ERMS cases, followed with ARMS and pleomorphic RMS with 6 patients each, while spindle cell RMS has 1 patient. There are 8 patients with not specified RMS. In terms of location, the extremities were the most common with a total of 13 patients (41.9%) divided into upper and lower extremities, followed by the head and neck region with 10 (32.2%) patients. Tumors with a size >10 cm were the most common, with 16 cases (51.6%). After radiotherapy, 21 (67.7%) cases were accounted as radiosensitive and 10 (32.3%) cases were radioresistant.

Table 2 shows the relationship between certain clinicopathological features of the patients. It shows that most ERMS appeared in children (n=8) and none that appeared in elderly, and vice versa, there was no non-ERMS cases that appeared in children. Meanwhile based on genders, no predilection regarding tumor locations.

**Table 1. Clinicopathological characteristics of patients.**

| Characteristics | Total (n=31)(%) |
|---|---|
| Sex | |
| Male | 18 (58.1) |
| Female | 13 (41.9) |
| Age (years) | |
| ≤18 | 10 (32.2) |
| 19-49 | 10 (32.2) |
| ≥50 | 11 (35.5) |
| Histology | |
| Embryonal RMS | 10 (32.2) |
| Alveolar RMS | 6 (19.4) |
| Pleomorphic RMS | 6 (19.4) |
| Spindle/sclerosing RMS NOS | 1 (3.2) |
| | 8 (25.8) |
| Location | |
| Head and neck | 10 (32.2) |
| Thorax | 4 (12.9) |
| Abdominal | 2 (6.4) |
| Extremities | 13 (41.9) |
| Upper | 6 (19.3) |
| Lower | 7 (22.6) |
| Perineal | 1 (3.2) |
| n/a | 1 (3.2) |
| Tumor size (cm) | |
| <5 | 4 (12.9) |

| Characteristics | Total (n=31)(%) |
|---|---|
| 5-10 | 11 (35.5) |
| >10 | 16 (51.6) |
| Outcome | |
| Radiosensitive | 20 (64.5) |
| Radioresistant | 11 (35.5) |

**RMS: rhabdomyosarcoma; NOS: not otherwise specified*

**Table 2. Relationship between certain clinicopathological features.**

| Characteristics | Sex | | Age | | | Total |
|---|---|---|---|---|---|---|
| | Male (n=18)(%) | Female (n=13)(%) | ≤18 (n=10)(%) | 19-49 (n=10)(%) | ≥50 (n=11)(%) | |
| Histology | | | | | | |
| Embryonal RMS | 5 (50) | 5 (50) | 8 (80) | 2 (20) | 0 | 10 |
| Alveolar RMS | 4 (66.7) | 2 (33.3) | 0 | 3 (50) | 3 (50) | 6 |
| Pleomorphic RMS | 3 (50) | 3 (50) | 0 | 2 (33.3) | 4 (66.7) | 6 |
| Spindle/sclerosing RMS NOS | 1 (100) | 0 | 0 | 1 (100) | 0 | 1 |
| | 5 (62.5) | 3 (37.5) | 2 (25) | 2 (25) | 4 (50) | 8 |
| Location | | | | | | |
| Head and neck | 4 (40) | 6 (60) | 5 (50) | 2 (20) | 3 (30) | 10 |
| Thorax | 2 (50) | 2 (50) | 1 (25) | 1 (25) | 2 (50) | 4 |
| Abdominal | 1 (50) | 1 (50) | 2 (100) | 0 | 0 | 2 |
| Extremities | 11 (84.6) | 2 (15.4) | 1 (7.7) | 7 (53.8) | 5 (38.5) | 13 |
| Perineal | 0 | 1 (100) | 0 | 0 | 1 (100) | 1 |
| n/a | 0 | 1 (100) | 1 (100) | 0 | 0 | 1 |

**RMS: rhabdomyosarcoma; NOS: not otherwise specified*

A comparison of the results between radiotherapy-sensitive and resistant tumors can be seen in table 3. In terms of age, the tumors in pediatric patients were more sensitive with a ratio of 3:2. Adult patients were equally numerous. While elderly patients were more sensitive with a ratio of 9:2. Based on subtype, 80% ERMS cases were sensitive, ARMS were equal in response, and 83.3% pleomorphic RMS were sensitive. 1 patient with spindle cell RMS was resistant, while RMS NOS were equal in response. Based on tumor size, tumors >10 cm were the most sensitive with a ratio of 13:3, followed by 5-10 cm and <5 cm.

**Table 3. Relationship Between Characteristics and Outcome**

| Characteristics | Outcome | | Total (n=31)(%) |
|---|---|---|---|
| | Radiosensitive (n=20)(%) | Radioresistant (n=11)(%) | |
| Age (years) | | | |
| ≤18 | 6 (60) | 4 (40) | 10 (32.2) |
| 19-49 | 5 (50) | 5 (50) | 10 (32.2) |
| ≥50 | 9 (81.8) | 2 (18.2%) | 11 (35.5) |
| Histology | | | |
| Embryonal RMS | 8 (80) | 2 (20) | 10 (32.2) |
| Alveolar RMS | 3 (50) | 3 (50) | 6 (19.4) |
| Pleomorphic RMS | 5 (83.3) | 1 (16.7) | 6 (19.4) |
| Spindle/sclerosing RMS | 0 | 1 (100) | 1 (3.2) |
| NOS | 4 (50) | 4 (50) | 8 (25.8) |
| Tumor size (cm) | | | |
| <5 | 2 (50%) | 2 (50%) | 4 (12.9) |

| Characteristics | Outcome | | Total (n=31)(%) |
|---|---|---|---|
| | Radiosensitive (n=20)(%) | Radioresistant (n=11)(%) | |
| 5-10 | 5 (54.5%) | 6 (45.5%) | 11 (35.5) |
| >10 | 13 (81.2%) | 3 (18.8%) | 16 (51.6) |

**RMS: rhabdomyosarcoma; NOS: not otherwise specified*

**Discussion**

Rhabdomyosarcoma (RMS) is a soft tissue neoplasm that originates from skeletal muscle mesenchymal cells. Although rare, it is the most common soft tissue sarcoma in children and adolescent.(Hornick JL, 2019) There are about 6 cases of RMS in every 1 million people worldwide.(Goldblum JR et al., 2020) RMS cases tend to be more common in patients in European and American countries than other regions. It is reported that the incidence of this case in the United States can reach 500 cases per year.(American Cancer Society, n.d.) While in parts of Asia, the number of RMS cases in the period 2002-2005 was recorded at 3.4 cases per 1 million people.(Wang X & et al, 2020) It is also noted that RMS is one of the most common sarcomas in South Asia, although it is not related with race or ethnicity.(Ahmad Z & et al, 2015) RMS can occur in all age ranges, although it is more common in pediatric patients. According to SIRS data from hospital in Bandung, it is estimated that within 5 years there were 52 cases of RMS originating from 1 center alone.(SIstem Infornmasi Rumah Sakit, 2023) In this study, there were 31 cases of patients with RMS who received complete radiotherapy. This number could have been higher, but was constrained by limited facilities in medical record storage and in the follow-up of patients who received therapeutic treatment.

Based on age incidence, RMS occurring in patients over 45 years of age is about 2% of all sarcomas, but can increase to up to 5% in the pediatric population.(Goldblum JR et al., 2020) This duality of incidence is influenced by differences in the subtypes of RMS. It is known that there are generally 4 subtypes of RMS, namely embryonal, alveolar, pleomorphic, and spindle cell/sclerosing. The embryonal RMS subtype (ERMS) is the most common compared to other subtypes, and is more common in the pediatric population. Meanwhile, alveolar RMS (ARMS) tends to be more common in the adult population.(World Health Organization, 2020) This is thought to be influenced by differences in the etiology and risk factors of each tumor. For example, ERMS cases are characterized by mutations of the *RAS* family, *NF*, or *TP53* genes.(Leuschner I & et al, 2003; World Health Organization, 2020) ARMS is characterized by *PAX3-FOXO1* and *PAX7-FOXO1* gene fusions which are not found in ERMS.(Martin-Giacalone BA et al., 2021; World Health Organization, 2020) The etiology of other RMS is influenced by mutations involving various genes, such as *VGLL2, SRF*, and *TEAD1*.(World Health Organization, 2020) There are also several other possible genetic disorders that can worsen the response of RMS to therapy, such as mutations in *TP53*, *c-Myc*, or *BCL2*.(Camero S & et al, 2022) In this study, most of RMS subtype was ERMS (32.2%), in which all pediatric RMS cases were either ERMS or NOS subtypes. Cases of ARMS, pleomorphic RMS, and spindle cell RMS were only found in adult or elderly patients.

Based on the location of the tumor, extremities were the most common followed by the head and neck. This predilection of the location of the tumor is in accordance with the reference, where ARMS and pleomorphic RMS cases are most common in the extremities, and ERMS is more common in the head and neck.(Goldblum JR et al., 2018) Meanwhile, large tumors size (>10 cm) were the most common cases found. This is thought to be mainly due to delays in early diagnosis. RMS, although an aggressive sarcoma, tends to have no specific clinical symptoms when it occurs in the early stages.(Khosla D & et al, 2015; Lindberg MR, 2019)

The difference in subtypes will affects the therapy plan that will be given to the patient. The dose of radiotherapy is influenced by the group or groups published by the Intergroup Rhabdomyosarcoma Studies (IRS) which is divided into 3 groups. Group I include complete resection as evidenced by histopathology. Group II is when the resection is microscopically incomplete, but macroscopically the tumor mass is no longer visible. Group III is macroscopically incomplete resection, where there is a residual tumor mass in-situ. In group I IRS, radiation therapy is not given if the histopathology is ERMS, but is given if the tumor is ARMS or other, as long as the patients age is 3 or older.(Raney RB & et al, 2001)

Radiotherapy is considered useful as an RMS therapy due to its ability to cause DNA damage that can kill cells. Radiation works by utilizing ionizing radiation, where the presence of charged particles will store enough energy in the tissue to cause DNA damage. The occurrence of DNA damage is then divided into single strand breaks (SSB) and double strand breaks (DSB). DSB is further divided into simple and complex depending on the type of strand breakage. Simple strand damage only occurs at each end of the strand, while complex damage occurs in several places and forms clusters that are very difficult to repair. This complex DNA damage is also exacerbated by oxidant effects and is a characteristic of radiotherapy-induced damage.(Baskar R & et al, 2014; Camero S & et al, 2022) Technically, radiotherapy can kill all types of solid tumor with maximum dosage, but it must be lowered to maintain tumor environment and not to kill a healthy cell. Hence, this paradigm is the causing nature of poor response of certain tumors.

The radiotherapy response is measured 3-dimensionally using radiological assessment, such as CT-scan, PET, or MRI. The results are determined by comparing the pre- and post-measures at a minimum of 8 weeks. RMS is considered radiosensitive if the tumor is proven to disappear or has a reduction of at least 33% of its original size. While radioresistant is determined if the tumor does not experience a significant reduction (<33%) or increases instead.(European paediatric Soft tissue sarcoma Study Group (EpSSG), 2012)

Despite the proven benefits of radiotherapy in suppressing the number of recurrences and deaths. RMS is one of a neoplasm that has a low sensitivity to radiotherapy, characterized by a therapeutic failure, relapse, or mortality. According to Frankart, et al, within 3 years after radiotherapy, there is a relapse rate of RMS in the head-neck that might reaches 75% of all cases.(Frankart A et al., 2021) Furthermore, Bergamaschi, et al through a European study reported that RMS patients aged over 18 years who had been given adequate radiotherapy only had a disease-free rate of 37% with a mortality rate of 42.8% in 5 years.(Bergamaschi L & et al, 2019)

Increasing tumor size or grade also contribute to decreased therapeutic response. Patients with ARMS subtype had a survival rate of 23.9% compared to 46.7% for non-alveolar. Lesion sized > 5 cm had a 5-year survival rate of 30% compared to ≤ 5 cm which was 55.9%.(Bergamaschi L & et al, 2019)

This study showed that although most (64.5%) cases were sensitive to radiotherapy, there were still 11 patients with resistant tumors. When examined further, the pediatric patient group (≤18 years old) had a good radiosensitivity level. This is consistent with the prognosis of RMS which tends to be better in young patients, as it is dominated by ERMS subtypes. The highest sensitivity level is found mostly in elderly. It is thought that this may be due to neglect by adult patients who tend to be in their productive age. The ERMS subtype was the most sensitive subtype as most of the tumors were sensitive. The other subtypes each had cases with radioresistant tumors. In RMS NOS, the sensitive response ratio is equal. This is consistent with the possibility that the NOS subtype is consists of ERMS and non-ERMS. As for size, small tumors had the worst response among other sizes, and got better as the size increased. This may occur because small tumors tend to be biopsied with residual tumors that are difficult to distinguish after radiotherapy. Whereas large tumors are excised which may still leave a lot of tissue in the body, making it easier to be measured. In the future, more RMS cases are needed in this research to clarify the clinicopathological picture of RMS in Indonesia. In addition, long-term follow-up assessment of patients is needed to assess the absence of relapse after radiotherapy.

## CONCLUSION

This study shows that there were 31 patients with rhabdomyosarcoma (RMS) who received radiotherapy. All subtypes of RMS of various sizes were found in these patients. A total of 11 cases experienced resistance to radiotherapy. The tumors were more sensitive to therapy in pediatric and elderly patients. Based on subtype, most ERMS cases were sensitive. Based on tumor size, the largest tumors were the most sensitive. Additional studies are needed to assess the long-term effects of radiotherapy or to assess specific genes for radiotherapy resistance.

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