The role of radiotherapy in Kimura’s disease: a multicenter systematic review of literature


Abstract. – OBJECTIVE: From a clinical point of view, Kimura’s disease is typically characterized by a subcutaneous mass occurring predominantly in the head and neck region. It occurs predominantly in young men of Asian descent, with a peak incidence in the second and third decades of life. However, KD has been also reported in other ethnic groups and in children. The most frequently used local treatments are surgical excision, radiotherapy, and surgical excision followed by radiotherapy. The aim of this multicenter systematic review is to highlight the available literature evidence about the outcome of RT in this setting.

MATERIALS AND METHODS: A systematic review of any relevant literature in the principal medical databases, such as PubMed, Scopus and Cochrane library, was conducted. The inclusion criteria were original articles specifically reporting about KD and RT, including both prospective and retrospective studies.

RESULTS: We were able to identify 11 studies, published from 1989 to 2021, eligible for inclusion in this review. Overall, data on 124 patients were recorded and are presented in this systematic review. The median recurrence rate, considering all patients, was 11% (ranging from 0% to 41.2%). In seven out of 11 studies, the relapse rate was less than 20%. Moreover, the relapse rate was 0% in four studies.

CONCLUSIONS: The results of this multicenter systematic literature review show that evidence on RT of KD is limited and derives only from retrospective studies. In this setting RT seems to be well-tolerated and able to produce very high response rates in unresected lesions and reasonable results in terms of local control both as an exclusive and adjuvant treatment.

Key Words: Kimura’s disease, Kimura disease, Radiotherapy, Radiation therapy.

Introduction

Eosinophilic hyperplastic lymphogranuloma is a benign disease which was first described in literature in 1937 by Chinese scientists. Later it was defined as Kimura’s disease (KD) in 1948 when a Japanese group of researchers published the definitive histologic features. From a clinical point of view, KD is typically characterized by a subcutaneous mass occurring predominantly in the head and neck (H&N) region. It occurs predominantly in young men of Asian descent, with a peak incidence in the second and third decade of life. However, KD has been also reported in other ethnic groups and in children. KD is a disorder associated with chronic inflammatory lesions of unclear etiology. In fact, some authors
claim possible association with allergic reaction, viral or parasitic interference with the immune system, and even with arthropod bites\textsuperscript{4}. In a few cases, KD may be associated with multiple organ involvement, affecting especially the renal function\textsuperscript{5}. However, in some series also the association with hepatitis, cardiovascular disease, and asthma have been reported\textsuperscript{6}. Although no cases of malignant transformation have been recorded yet, an active treatment is necessary being a spontaneous resolution described only in a single case report\textsuperscript{7}. Several therapeutic options are suggested in the literature, such as steroids, mitomycin C and other drugs\textsuperscript{8}. However, the most frequently used local treatments are surgical excision, radiotherapy (RT), and surgical excision followed by RT\textsuperscript{9}.

However, there is only little evidence on this topic and systematic reviews of the literature are lacking, in particular on the role of RT in KD. In fact, only limited data has been published in English literature on the matter, and no systematic review has ever addressed the role of RT in the therapeutic strategy; therefore, the aim of this multicenter systematic review is to highlight the available literature evidence about the outcome of RT in this setting.

**Materials and Methods**

The search process was managed referring to the PRISMA guidelines as shown in Figure 1\textsuperscript{10}. A systematic review of any relevant literature in the principal medical databases, such as PubMed, Scopus and Cochrane library, was conducted. The search strategy included a combination of the following terms: “Kimura disease” or “Kimura’s disease” or “eosinophilic hyperplastic lymphogranuloma” and “radiotherapy” or “radiation therapy”. The time interval included all published articles present in the databases from their inception until January 2021. The inclusion criteria were original articles specifically reporting about KD and RT, including both prospective and retrospective studies. Reviews, letters to the editor, articles not in English, conference papers, case reports, and papers with mixed cases other than KD were excluded. Two independent authors, a radiation oncologist (BF) and an otorhinolaryngologist (AL), screened citations in titles and abstracts to identify appropriate papers. Eligible citations were retrieved for full-text review. Uncertainties about their inclusion in the review were considered by another team composed of 3 additional radiation oncologists (VL-CC-AR) who performed an independent check.

Finally, a multicenter Master committee (FB – Sassari, AV – Milano, LV – Ancona, FD – Campobasso, AGM – Bologna, MAG and LT – Rome) composed by senior experts in external beam RT, experts in interventional RT and senior otorhinolaryngologist, performed a definitive check and the approval of the review.

**Results**

We were able to identify 11 studies, published from 1989 to 2021, eligible for inclusion in this review. All analyzed studies had a retrospective design and all of them were published by Asian authors. Overall, data on 124 patients were recorded and are presented in this systematic review. A detailed and complete list of all collected data is available in Table I. The typical patient referred for RT was aged between the 2\textsuperscript{nd} and 3\textsuperscript{rd} decade (median: 33 years) and with a strong male prevalence (range: 69-100%; median: 86%). The median follow-up time ranged from 1.5 to 13 years (median: 4). In four series\textsuperscript{8,13,14,22}, mainly the older ones, RT was prescribed in some cases as exclusive treatment. However, in most recent and numerous reports\textsuperscript{6,11,12,16,18,19,20} RT was used as postoperative therapy. The median largest size of treated lesions was 9.5 cm (with lesions up to 18 cm). The response rate in unresected patients ranged between 92.9% and 100% (median: 100%). The median recurrence rate, considering all patients, was 11% (ranging from 0% to 41.2%). In seven out of 11 studies, the relapse rate was less than 20%. Moreover, the relapse rate was 0% in four studies. The median recurrence rate was 8.3% (range: 0-41.2%) and 19.9% (range: 0-40%) in the series where all patients were resected and the studies, respectively. The RT schedules used in the different series were not uniform. In fact, the delivered doses ranged from 13 Gy to 56 Gy. However, in most of the reports presenting this data (7 out of 9) the delivered dose was between 20 Gy and 45 Gy with standard fractionation. Of the 11 analyzed studies, only the series described by Ye et al\textsuperscript{7}, including only lesions in the H\&N site, reported some side effects (slight xerostomia).

**Discussion**

KD is an inflammatory disease including a wide range of clinical presentations. Several fea-
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Characteristics of this disease still need to be investigated, such as etiopathogenesis which has remained elusive even though the most recent evidence suggests an immune-mediated etiology.

From the histopathological point of view the largely predominant feature is the presence of lymphoid hyperplasia and capillaries leading to the development of well-formed follicles associated with fibrosis. Therefore, the three key elements of KD are white blood cells (mainly including lymphocytes and eosinophils), capillaries, and connective tissue.

International classifications of KD are lacking. Its usual presentation is represented by lateral neck lymphadenopathies and subcutaneous masses. However, other sites in the H&N region were described, such as oral mucosa, nasal cavity, bone, muscle, salivary glands, orbit, lacrimal gland, and tympanic membrane.

KD should not be underestimated considering that, even if considered a benign disease, in some cases it may cause severe morbidity with different inflammatory symptoms according to the involved site. In addition, with recurrence rate reaching in some series up to 80% of cases, also a prolonged follow-up is recommended.

Furthermore, in a few cases KD may be regarded also as a systemic disease with multiple organ involvement, such as lymph nodes in sites other than the H&N region, blood vessels, and kidneys. Moreover, up to 16% of patients may present with proteinuria.

Therefore, before confirming the diagnosis of KD, lymphoproliferative diseases and various

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**Figure 1.** Search strategy.
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Number of patients</th>
<th>Mean age</th>
<th>Gender (Male/Female)</th>
<th>Number of lesions size</th>
<th>Largest size (cm)</th>
<th>Prior surgery</th>
<th>Prior steroids</th>
<th>Dose and fractionation</th>
<th>Response</th>
<th>Recurrence</th>
<th>Side effects</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itami et al</td>
<td>Japan</td>
<td>1989</td>
<td>10</td>
<td>34</td>
<td>90%/10%</td>
<td>Single 90% Multiple 10%</td>
<td>&gt;6</td>
<td>0</td>
<td>80%</td>
<td>13 Gy - 56 Gy</td>
<td>100%</td>
<td>40%</td>
<td>None</td>
<td>Up to 13 years</td>
</tr>
<tr>
<td>Kim et al</td>
<td>Korea</td>
<td>1997</td>
<td>9</td>
<td>23</td>
<td>78%/22%</td>
<td>Single 56% Multiple 44%</td>
<td>12</td>
<td>100%</td>
<td>n.a.</td>
<td>21.6 Gy - 45 Gy (median: 30 Gy) 1.8 Gy - 2 Gy/fx</td>
<td>n.a.</td>
<td>11%</td>
<td>None</td>
<td>4 years</td>
</tr>
<tr>
<td>Hareyama</td>
<td>Japan</td>
<td>1998</td>
<td>20</td>
<td>32</td>
<td>95%/5%</td>
<td>Single 85% Multiple 15%</td>
<td>18</td>
<td>65%</td>
<td>25%</td>
<td>20 Gy - 44 Gy</td>
<td>100%</td>
<td>25.9%</td>
<td>None</td>
<td>4 years</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Korea</td>
<td>2006</td>
<td>14</td>
<td>22</td>
<td>86%/14%</td>
<td>Single 71% Multiple 29%</td>
<td>11</td>
<td>43%</td>
<td>71%</td>
<td>20 Gy - 45 Gy 1.8 Gy - 5 Gy/fx</td>
<td>92.9%</td>
<td>14%</td>
<td>None</td>
<td>5 years</td>
</tr>
<tr>
<td>Chitapanarux et al</td>
<td>Thailand</td>
<td>2007</td>
<td>8</td>
<td>39</td>
<td>75%/25%</td>
<td>Single 87% Multiple 13%</td>
<td>n.a.</td>
<td>63%</td>
<td>n.a.</td>
<td>30 Gy - 40 Gy</td>
<td>100%</td>
<td>0</td>
<td>None</td>
<td>2 years</td>
</tr>
<tr>
<td>Takeishi et al</td>
<td>Japan</td>
<td>2007</td>
<td>2</td>
<td>32</td>
<td>100%/0%</td>
<td>Single 100%</td>
<td>n.a.</td>
<td>100%</td>
<td>50%</td>
<td>30 Gy</td>
<td>n.a.</td>
<td>0</td>
<td>None</td>
<td>2 years</td>
</tr>
<tr>
<td>Chen et al</td>
<td>China</td>
<td>2015</td>
<td>17</td>
<td>33</td>
<td>84%/16%</td>
<td>n.a.</td>
<td>8</td>
<td>100%</td>
<td>30%</td>
<td>36 Gy - 40 Gy 2 Gy/fx</td>
<td>n.a.</td>
<td>41.2%</td>
<td>None</td>
<td>1.5 years</td>
</tr>
<tr>
<td>Ye et al</td>
<td>China</td>
<td>2017</td>
<td>24</td>
<td>41</td>
<td>87%/13%</td>
<td>Single 63% Multiple 37%</td>
<td>n.a.</td>
<td>100%</td>
<td>n.a.</td>
<td>20 Gy - 50 Gy2</td>
<td>n.a.</td>
<td>8.3%</td>
<td>Slight Xerostomia</td>
<td>4 years</td>
</tr>
<tr>
<td>Jiang et al</td>
<td>China</td>
<td>2017</td>
<td>10</td>
<td>35</td>
<td>69%/31%</td>
<td>Single 59% Multiple 41%</td>
<td>&gt;5</td>
<td>100%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>22%</td>
<td>None</td>
<td>7 years</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>China</td>
<td>2019</td>
<td>6</td>
<td>27</td>
<td>87%/13%</td>
<td>Single 26% Multiple 74%</td>
<td>12</td>
<td>100%</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0</td>
<td>None</td>
<td>Up to 30 years</td>
</tr>
<tr>
<td>Zhang et al</td>
<td>China</td>
<td>2020</td>
<td>4</td>
<td>44</td>
<td>84%/16%</td>
<td>Single 79% Multiple 21%</td>
<td>7</td>
<td>100%</td>
<td>n.a.</td>
<td>36 Gy - 45 Gy 2 Gy/fx</td>
<td>n.a.</td>
<td>0</td>
<td>None</td>
<td>Up to 12 years</td>
</tr>
</tbody>
</table>

Legend: fx: fraction; H&N: Head and Neck; n.a.: not available
rheumatologic disorders (Wegener’s granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, and rheumatoid arthritis), which can be associated with subcutaneous and lymph nodes inflammation, should be excluded 17.

The most frequently used therapeutic option in KD is surgical resection. Also, steroids have been commonly used as therapeutic strategy either in multiple site involvement or with the aim to reduce bulky lesions before considering alternative approaches 18. RT may be beneficial because it has been demonstrated that the three major histologic components of KD (cellular, fibro-collagenous and vascular) respond favorably to irradiation 19.

RT may play a role both as an exclusive and an adjuvant treatment modality, always with a thorough discussion of indications in a multidisciplinary setting. Exclusive treatments were more often indicated in the past 8,13,14,22, with the aim of avoiding severe cosmetic damage and/or in cases of recurring disease after surgery. However, in most recent series 6,11,12,16,18,19,20 RT has been more often used in an adjuvant setting, when the initial disease is incompletely resected and when there are contraindications to systemic treatments, such as steroids 20. All this would be in analogy with the established evidence on the usefulness of postoperative RT in H&N cancers in reducing the local recurrence rates 21 especially in organ sparing approaches 22.

It should be emphasized that no uniform response criteria were used across the different papers included in this review. In fact, in some cases the response was assessed clinically whereas in other studies the response evaluation was based on radiological assessment. In addition, resolution of the disease in most cases did not explicitly include data on systemic therapies discontinuation or reduction. For such reasons it is not easy to achieve clear conclusions from data shown in Table I. However, it can be seen that the clinical response rate obtained with RT was very high (92.2%-100%). The local control rates, expressed as ranges, are substantially similar between series in which all patients underwent surgery (0%-41.2%) compared to the others (0%-40%). These data seem to generate some doubts about the need to submit all KD patients to up-front surgery.

Regarding the optimal RT dose there is no consensus among the different authors as shown by the wide range of the reported doses. In particular, in one study where the main focus was to identify the threshold dose for local control and the result was that no association was found between total dose and local control 21.

Some additional considerations should be done about tolerance and side effects reported in the analyzed papers. In fact, in almost all cases no toxicity was reported after RT and only in one series some cases of slight xerostomia were recorded. The reasons of these low toxicity rates might be related to the relevant grade of local inflammation at diagnosis, which could have hindered the differential diagnosis between the underlying disease signs and the side effects. Another possible explanation is the retrospective design of the analyzed studies which may have caused some toxicity under-recording.

Finally, an additional explanation of the low incidence and severity of side effects can come from the total delivered dose that was quite low in most series. Due to the rarity of KD, it could be reasonable to promote the design of large databases based on international networks following the renewed interest of researchers in the field about the association of RT and bending disorders 24.

This systematic review has allowed us to provide the most comprehensive and up-to-date synthesis of the available data about KD and RT thus highlighting the potential benefits of RT, which is well tolerated and associated with good response rates in unresected lesions, however, additional investigations are desirable in the future.

**Conclusions**

The results of this multicenter systematic literature review show that evidence on RT of KD is limited and derives only from retrospective studies. In this setting, RT seems to be well tolerated and able to produce very high response rates in unresected lesions and reasonable results in terms of local control both as an exclusive and adjuvant treatment. Further studies are needed to identify the best treatment or treatment combination based on disease and patient characteristics.

**Conflict of Interest**

The Authors declare that they have no conflict of interest.

**References**


