

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

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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 ev-

idence 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 scientists¹. Later it was defined as Kimura's disease (KD) in 1948 when a Japanese group of researchers published the definitive histologic features². 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 children³. 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 bites⁴. In a few cases, KD may be associated with multiple organ involvement, affecting especially the renal function⁵. However, in some series also the association with hepatitis, cardiovascular disease, and asthma have been reported⁶. 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 report⁷. Several therapeutic options are suggested in the literature, such as steroids, mitomycin C and other drugs⁸. However, the most frequently used local treatments are surgical excision, radiotherapy (RT), and surgical excision followed by RT⁹.

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 1¹⁰. 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 2nd and 3rd 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^{8,13,14,22}, mainly the older ones, RT was prescribed in some cases as exclusive treatment. However, in most recent and numerous reports^{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 al⁹, 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-

tures 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 etiology¹¹.

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 tissue¹².

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 cavi-

ty, bone, muscle, salivary glands, orbit, lacrimal gland, and tympanic membrane¹³.

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 site¹⁴. In addition, with recurrence rate reaching in some series up to 80% of cases, also a prolonged follow-up is recommended¹⁵.

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 proteinuria¹⁶.

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

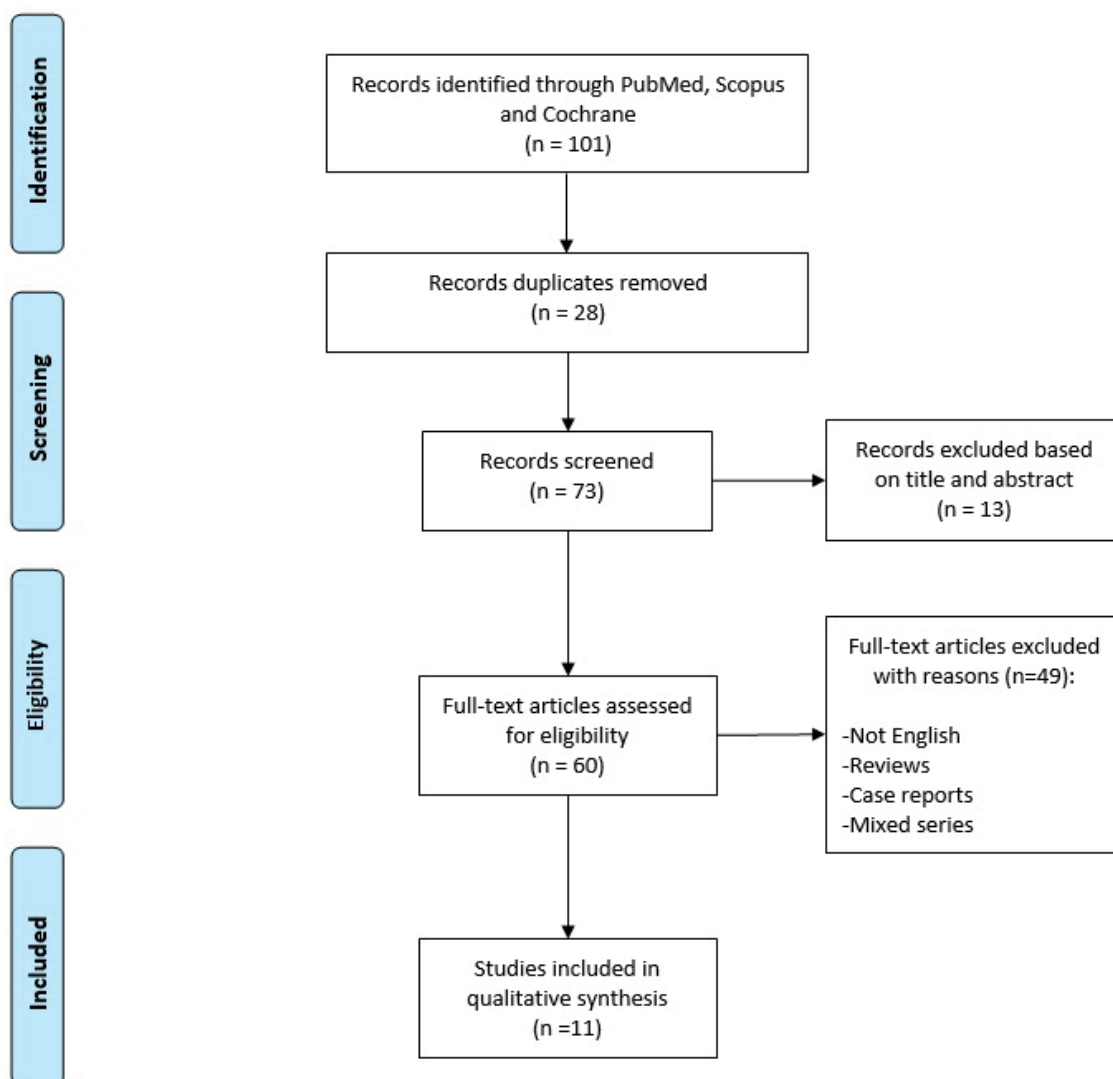


Figure 1. Search strategy.

Table I. Features of patients and relative treatment details.

Author	Country	Year	Number of patients	Mean age	Gender (Male/Female)	Initial site	Number of lesions size	Largest size (cm)	Prior surgery	Prior steroids	Dose and fractionation	Response	Recurrence	Side effects	Median follow-up
Itami et al ¹⁴	Japan	1989	10	34	90%/10%	H&N 100%	Single 90% Multiple 10%	>6	0	80%	13 Gy - 56 Gy	100%	40%	None reported	Up to 13 years
Kim et al ¹⁹	Korea	1997	9	23	78%/22%	H&N 89% Other 11%	Single 56% Multiple 44%	12	100%	n.a.	21.6 Gy - 45 Gy (median: 30 Gy) 1.8 Gy - 2 Gy/fx)	n.a.	11%	None reported	4 years
Hareyama	Japan	1998	20	32	95%/5%	H&N 90% Other 10%	Single 85% Multiple 15%	18	65%	25%	20 Gy - 44 Gy	100%	25.9%	None reported	4 years
Chang et al ²³	Korea	2006	14	22	86%/14%	H&N 86% Other 14%	Single 71% Multiple 29%	11	43%	71%	20 Gy - 45 Gy 1.8 Gy - 5 Gy/fx	92.9%	14%	None reported	5 years
Chitapanarux et al ¹³	Thailand	2007	8	39	75%/25%	H&N 100%	Single 87% Multiple 13%	n.a.	63%	n.a.	30 Gy - 40 Gy	100%	0	None reported	2 years
Takeishi et al ¹⁸	Japan	2007	2	32	100%/0%	H&N 100%	Single 100%	n.a.	100%	50%	30 Gy	n.a.	0	None reported	2 years
Chen et al ⁶	China	2015	17	33	84%/16%	n.a.	n.a.	8	100%	30%	36 Gy - 40 Gy 2 Gy/fx	n.a.	41.2%	None reported	1.5 years
Ye et al ²⁰	China	2017	24	41	87%/13%	H&N 100%	Single 63% Multiple 37%	n.a.	100%	n.a.	20 Gy - 50 Gy2	n.a.	8.3%	Slight Xerostomia	4 years
Jiang et al ¹²	China	2017	10	35	69%/31%	H&N 81% Other 19%	Single 59% Multiple 41%	>5	100%	n.a.	n.a.	n.a.	22%	None reported	7 years
Zhang et al ¹⁶	China	2019	6	27	87%/13%	H&N 63% Other 37%	Single 26% Multiple 74%	12	100%	n.a.	n.a.	n.a.	0	None reported	Up to 30 years
Zhang et al ¹¹	China	2020	4	44	84%/16%	H&N 71% Other 29%	Single 79% Multiple 21%	7	100%	n.a.	36 Gy - 45 Gy 2 Gy/fx	n.a.	0	None reported	Up to 12 years

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 excluded¹⁷.

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 approaches¹⁸. 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 irradiation¹⁹.

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 steroids²⁰. 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 rates²¹ especially in organ sparing approaches²².

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 control²³.

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 disorders²⁴.

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 interests.

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