Comparison of Local Recurrence Rate of Three Treatment Modalities for Kimura Disease

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Abstract: Eosinophilic hyperplastic lymphogranuloma, also known as Kimura disease, is a benign and chronic inflammatory condition, predominantly involving the head and neck region. Surgical excision, radiotherapy (RA), surgical resection combined with low-dose postoperative radiotherapy and oral corticosteroids are 4 treatment modalities reported to control this disease effectively. Local recurrence, however, is common and the optimum treatment for Kimura disease is controversial. Thus, the present meta-analysis was performed to identify the treatment modality associated with the lowest local recurrence. Electronic databases (Cochrane Library, Wiley Online Library, PubMed, Chinese National Knowledge Infrastructure, and Wanfang Data) were searched. Data were also obtained from other sources such as related references and communication with the relevant authors. Two reviewers screened the literature according to preselected criteria. All studies involving different treatments for Kimura disease were collected. After data extraction and research quality assessment, the meta-analysis of 22 studies involving 570 patients was conducted using STATA 12.1 software. Meta-analysis revealed that administration of RA or surgical excision alone were inferior in controlling local recurrence compared with surgical resection combined with postoperative RA (risk ratio (RR) = 2.72; 95% confidence interval (CI), 1.47–5.04 and RR = 4.72; 95% CI, 2.53–8.82). Surgical excision alone did not show significant advantage in controlling local recurrence compared with RA alone (RR = 2.13; 95% CI, 0.88–5.17). Surgical resection combined with postoperative RA is superior to either surgery or RA alone in treating Kimura disease. More large scale prospective randomized controlled trials, however, should be conducted to assess the long-term effects and safety issues.

Key Words: Kimura disease, meta-analysis, radiotherapy, surgical excision, surgical resection combined with postoperative radiotherapy

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Kimura disease, which was first described by a Chinese surgeon named Kim, is widely recognized as a benign but chronic inflammatory condition that occurs predominantly in young Asian men.[1] Kim et al designated this disease "eosinophilic hyperplastic lymphogranuloma." Subsequently, Kimura et al[2] described the histopathologic features of this condition, which has since become widely known as Kimura disease.

Kimura disease is a rarely reported disorder, with the majority of clinical investigations of this disease published in Asian literature. Owing to its rarity, most of the clinical studies are case reports or series studies.[3–11] With regard to treatment modalities, the lack of large scale systemic clinical studies on a variety of therapies such as surgical excision (SE), radiotherapy (RA), surgical resection combined with low-dose postoperative radiotherapy [surgical resection combined with radiotherapy (SRRA)] and corticosteroid has led to controversy regarding the optimum treatment for Kimura disease. Moreover, Kimura disease typically involves subcutaneous tissue without well-defined boundaries[12] making effective SE of the lesions problematic. Thus, a combination of surgery and postoperative intervention seems to be a reasonable approach. No investigations comparing the outcomes of these mainstream treatments, however, have yet been reported. Therefore, we conducted a meta-analysis to evaluate the prognosis and outcomes of 3 main treatment modalities; SE, RA, and SRRA.

MATERIAL AND METHODS

Literature Search

The Cochrane Library, Wiley Online Library, PubMed, Chinese National Knowledge Infrastructure were searched by 2 investigators (Peng and Tai) independently, without language and date restrictions using the searching algorithm: Kimura disease, eosinophilic hyperplastic lymphogranuloma, and (or) treatment, RA.

Eligibility Criteria

Clinical studies associated with at least 2 treatment modalities for Kimura disease and adequate follow-up outcomes were considered eligible.

Studies without treatment descriptions or follow-up information were excluded. Case reports and studies involving a single treatment were also excluded because of the small study population.

Data Extraction and Outcomes

Following the Meta-analysis of Observational Studies in Epidemiology checklist, 2 investigators reviewed and extracted all the data from eligible studies independently. For each eligible study, the following details were recorded: country of origin, author's names, year of publication, number of patients undergoing each treatment modality, duration of follow-up, and recurrence rate, which was the main outcome parameter. Local recurrence was

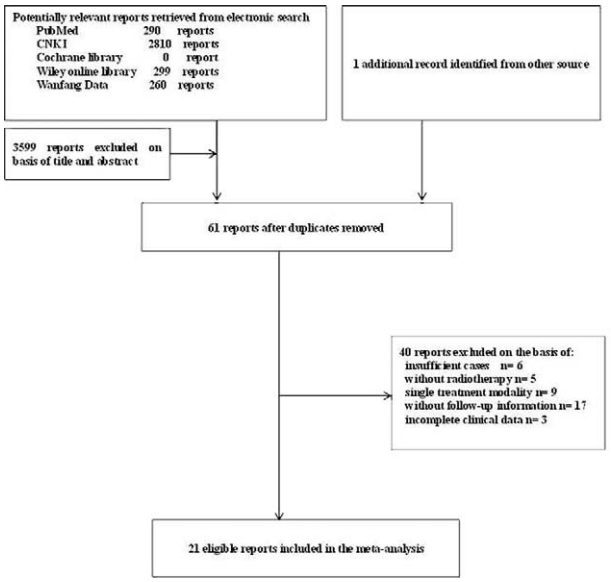

FIGURE 1. Summary of report selection process.

defined as newly detected swelling within, or neighboring, the previous focal field of intervention. On encountering discrepancies, another investigator was consulted to reach a consensus.

Methodological Quality Assessment

Two investigators assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale for cohort studies, which encompasses 3 parameters: selection (a maximum score of 4), comparability (a maximum score of 2), and outcome (a maximum score of 3). Thus, using these criteria, a study of the highest quality will gain a score of 9.

Statistical Analysis

All statistical analyses were performed using STATA statistical software (version 12.1; Stata Corp LP, College Station, TX). Four-fold tables were listed and risk ratios (RR) of 2 treatments were calculated for each study. Risk ratio heterogeneity was analyzed by χ^2 tests. A fixed effects model was used to calculate pooled RRs and their 95% confidence intervals (CI) for homogeneous studies and a random effects model was used for heterogeneous studies.

RESULTS

Eligible Study Characteristics

Electronic searches yielded 3659 reports: 2810 from the Chinese National Knowledge Infrastructure, 260 from Wan Fang Data, 290 from PubMed, 299 from Wiley online library, and 0 from the Cochrane Library. Of these Chinese and English reports, 20 were considered eligible,[13–33] 1 report was included after the author shared more follow-up details by email[34] and 1 unpublished study conducted on Kimura disease treatment by our group was also included. In total, 22 reports of 570 patients were included in our meta-analysis (Fig. 1). Of these reports, 3 were published in English, 18 were published in Chinese, and the unpublished study will be submitted for publication in English. All 22 reports described at least 2 treatment modalities, including RA. The detailed characteristics of eligible studies are summarized in Table 1.

Meta-Analysis

Our meta-analysis focused on comparing the recurrence rates among patients treated by SE and RA alone (SE versus RA), RA alone and SRRA (RA versus SRRA), and SE alone and SRRA (SE versus SRRA).

Radiotherapy Versus Surgical Resection Combined With Radiotherapy

Figure 2 shows the results of meta-analysis for recurrent outcomes of RA alone and SRRA (RA versus SRRA). No significant difference in data heterogeneity was detected ($I^2 = 0.0\%$, $P > 0.01$); therefore, a fixed effects model was employed. The pooled RR was 2.718 (95% CI 1.467–5.037), indicating that RA treatment alone increased the local recurrence rate by 1.718 times compared with SRRA. Thus, SRRA resulted in a better prognosis than RA alone.

Surgical Excision Versus Surgical Resection Combined With Radiotherapy

Figure 3 shows the results of meta-analysis for recurrent outcomes of SE and surgical resection combined with radiotherapy (SE vs. SRRA). No significant difference in data heterogeneity was detected ($I^2 = 31.3\%$, $P > 0.01$); therefore, a fixed effects model was employed. The pooled RR was 4.722 (95% CI, 2.528–8.819), indicating that the local recurrence rate associated with SE alone was 4.722 times greater than that associated with SRRA. Thus, SRRA delivered a better prognosis than SE alone.

Surgical Excision Versus Radiotherapy

Figure 4 shows the results of meta-analysis for recurrent outcomes of SE and radiotherapy alone (SE versus RA). A significant difference in data heterogeneity was detected ($I^2 = 79.9\%$, $P < 0.01$); therefore, a random effects model was employed. The pooled RR was 2.13 (95% CI, 0.88–5.17). Because of including 1 in the 95% CI, the RR value had no statistical significance; thus, no significant difference in the risk of local recurrence associated with SE and RA alone were detected.

Publication Bias

Figure 5 shows relative symmetry in 3 funnel plots for the comparisons, indicating that there was no publication bias among the included studies. Furthermore, application of Begg rank correlation test and Egger linear regression method [RA versus SRRA (Begg, $P = 1$; Egger, $P = 0.058$); SE versus SRRA (Begg, $P = 1$; Egger, $P = 0.433$); SE versus RA (Begg, $P = 0.649$; Egger, $P = 0.036$)] confirmed the absence of publication bias.

DISCUSSION

Kimura disease is a benign inflammatory condition with a favorable prognosis. Malignant transformation has not been reported in the literature even in cases of multiple recurrences. Nevertheless, recurrence is common after clinical intervention; thus, the efficacy of each treatment is typically evaluated on the basis or recurrence rate. Recurrence data were available for all our eligible reports. In clinical practice, SE, RA and surgical resection combined with low-dose postoperative radiotherapy are the 3 main treatment modalities for this disease entity.

To date, several interventions have been reported in including SE, RA, and steroid therapy;[11,35] however, there is no current consensus on the optimal treatment for this disease. For diagnostic and therapeutic purposes, SE is the usual approach, although the lack of a defined lesion margin in clinicopathologic examinations.[12] This makes it difficult to achieve a negative margin by SE alone,

TABLE 1. Characteristics of Eligible Studies

Author	Year	No. of Subjects	Age (Years)	Site	Follow-Up Interval	Score of NOS
He Jia-lin	1984	20	6–47	PR, PAR, eyelid, lip, neck, armpit, wrist, TW, groin	1–23 years	8
Liu Wen-bin	1987	23	5–49	Not reported	4 months–19 years	8
He zhixiu	1990	54	5–61	PR, PAR, BR, SR, neck, scalp	1–8 years	8
Kim	1997	17	10–66 (median 23)	Maxillofacial region, neck	1–9 years	8
He Jian-li	1999	21	13–60 (median 40)	PR, lymph node, bone	Undetailed	6
Hu Jing-yu	2000	24	4–62 (mean 42)	PR, SR, neck, SCR, armpit, groin, elbow	Undetailed	6
Cai Jian-bo	2000	12	14–60 (mean 32)	PR, BR, SMR, neck	3–17 years	8
Liang Li-rong	2001	65	7–68 (median 36.5)	PR, SR, neck, SMR, ZR	2–5 years	8
Yang Liuq-in	2003	8	15–40 (median 23)	PR, SR, neck, groin	Undetailed	6
Yu Wen-qiao	2003	34	2–79 (mean 37.4)	PR, SR, BR, lip, ZR	1–5 years	8
Zhang Wiao-jun	2004	15	17–68 (mean 37.9)	PR, SR, BR, IOR,	Undetailed	6
Xia Ai-juan	2005	30	30–60	PR, PAR, BR, SR, neck	3–5 years	8
Chen Wei-jun	2005	24	14–72 (mean 46)	PR, BR, SR, NC	2–5 years	8
Chang	2006	23	12–61	PR, PAR, lymph node	0.6–10.2 years	8
Han Lin	2007	41	10–76 (mean 39.9)	PR, SR, BR, neck, SMR	2–14 years	8
Takeishi	2007	11	16–48 (mean 31.5)	PR, PAR, TR, FR	1–28 years (mean 5.3 years)	8
Si Yameng	2008	28	13–66 (median 40)	PR, SR, BR, SMR, TR, FR	Undetailed	6
Li Dongsheng	2009	23	7–64 (median 33)	PR, BR, eyelid, SR, neck, groin, TW	1–3 years	8
Yan Xiang	2009	17	34–69 (mean 38.9)	PR, SR, TR, limbs, truncus	2–3 years	8
Zhang Ying-jun	2012	20	15–69 (mean 38)	PR, SR, BR, neck, groin	4–115 months (35 months)	8
Zhao Xin	2014	14	2–67 (mean 28)	PR, SR, SMR, neck, groin	1–13 months	8
Ye Peng	2014	46	5–78 (median 41)	PR, SR, BR, neck, FR	2 months–20 years (42 months)	8

BR, buccal region; FR, frontal region; IOR, infraorbital region; NC, nasal cavity; NOS, Newcastle-Ottawa Scale; PAR, postauricular region; PR, parotid region; SCR, supraclavicular region; SMR, submental region; SR, submandibular region; TR, temporal region; TW, thoracic wall; ZR, zygomatic region.

and accounts for the recurrence rates up to 25% associated with this modality. In contrast, Kimura disease responds well to irradiation and Hareyama et al[35] reported that a 90% local control rate was achieved by using low dosage of RA. Some Chinese authors reported that SE combined with postoperative RA was associated with a much lower local recurrence rate than that achieved with surgery or RA alone.[24,25,28] As an auxiliary treatment, postoperative RA plays an important role in controlling the residual lesion and achieving a lower recurrence and no malignancy resulting from irradiation has been reported to date. Nakahara et al[36] reported that steroid therapy can control subcutaneous lesions and lymphadenopathy in Kimura disease, but local recurrence occurred frequently during the period of steroid dose tapering. This indicates that steroid therapy alone does not cure Kimura disease; therefore, steroid therapy is carried out as a second-line treatment in consideration of the risks of relapse and side-effects. At the time of this writing, SE or RA alone and SRRA are the 3 most commonly applied modalities of treatment for Kimura disease.

To our knowledge, this is the first meta-analysis of the therapeutic efficacy of different treatment modalities for Kimura disease. Considering the low incidence of this disease and the small patient population, few reports included a statistical analysis of the differences between treatments; thus, a meta-analysis of the local recurrence rates associated with the 3 most common treatments for

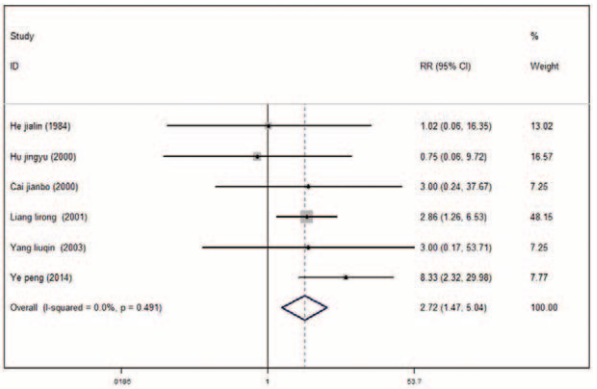

FIGURE 2. Meta-analysis of comparison of recurrence rates associated with treatment by radiotherapy alone and surgical resection combined with radiotherapy. Each study is characterized by the estimated risk ratio and 95% confidence interval (extended line). The overall risk ratios and 95% confidence intervals are represented by the diamond. Values >1 indicate that SE is associated with a higher recurrence rate than surgical resection combined with radiotherapy.

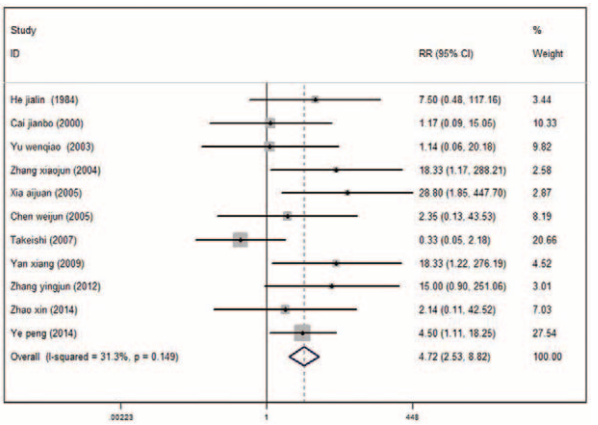

FIGURE 3. Meta-analysis of comparison of recurrence rates associated with treatment by surgical excision alone and surgical resection combined with radiotherapy. Each study is characterized by the estimated risk ratio and 95% confidence interval (extended line). The overall risk ratios and 95% confidence intervals are represented by the diamond.

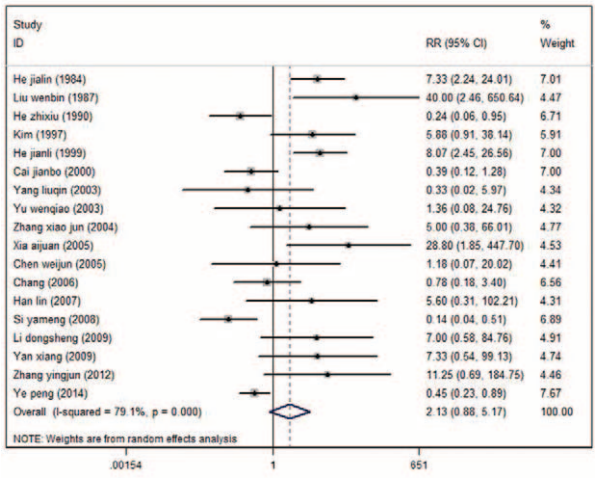

FIGURE 4. Meta-analysis of comparison of recurrence rates associated with treatment by radiotherapy and surgical excision alone. Each study is characterized by the estimated risk ratio and 95% confidence interval (extended line). The overall risk ratios and 95% confidence intervals are represented by the diamond.

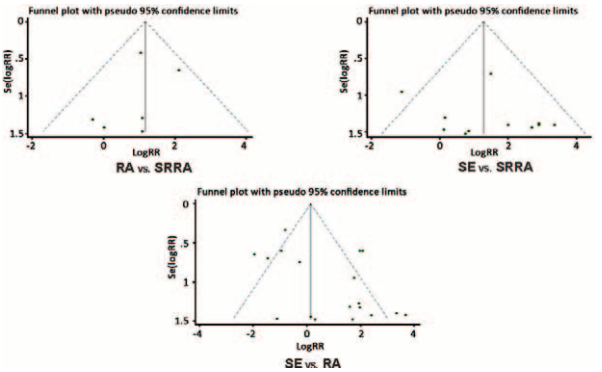

FIGURE 5. Funnel plot based on risk ratio for association between radiotherapy and surgical resection combined with radiotherapy, surgical excision and surgical resection combined with radiotherapy, surgical excision and radiotherapy.

Kimura disease will provide important information regarding the choice of the most effective treatment modality. Nevertheless, some limitations of our meta-analysis should be noted. First, the available treatment and follow-up data for Kimura disease is limited, because this disease is rare and predominantly occurs in Asian populations. The population of 639 patients involved in our meta-analysis is considered relatively small for a definitive conclusion. Second, the follow-up period of each study varied, with an absence of the detail of follow-up duration in a few of these studies. These limitations are likely to make our conclusion less persuasive. Finally, although Kimura disease can present as single or multiple lesions in the head and neck or other regions, comparisons of therapeutic outcomes between single and multiple lesions have not yet been reported, and the differences between these variations of Kimura disease remain to be elucidated.

Our meta-analysis supports the conclusion that the SRRA treatment modality for Kimura disease achieves the lowest local recurrence rate. This suggests that surgical resection (for the purposes of histopathologic diagnosis and lesion-removal) and postoperative low-dose irradiation should be carried out for patients diagnosed with Kimura disease, in clinical practice.

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