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Management and Future Therapeutic Perspectives of Classic Kaposi's Sarcoma: An Evidence-Based Review

Nerina Denaro[1,*], Alice Indini[2,*], Lucia Brambilla[3], Angelo Valerio Marzano[3,4], Ornella Garrone[1,*], Athanasia Tourlaki[3,*]

[1]Medical Oncology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [2]Melanoma Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

*These authors contributed equally to this work

Correspondence: Nerina Denaro, Medical Oncology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Francesco Sforza 35, Milan, 20122, Italy, Tel +390255032660, Email nerina.denaro@policlinico.mi.it

Background: Kaposi sarcoma (KS) is a cutaneous neoplasm of endothelial origin. The causative agent is the human herpes virus-8 (HHV-8) which, combined with an immune system impairment, causes cell proliferation. To date, high-quality evidence and treatment recommendations for the management of KS are confined to the acquired immune deficiency syndrome (AIDS)-related KS, while the clinical approach to the treatment of classic KS (CKS) is based on small retrospective case series and the experience of clinicians in selected referral centers.

Materials and Methods: A search of the English literature was conducted through PubMed/MEDLINE databases for studies regarding CKS diagnosis, staging, and treatment, published between January 1990 and September 2023.

Results: Overall, 122 out of 565 articles were selected. Based on the results of this literature review, we proposed indications regarding the recommended flow chart for diagnosis, staging, and follow-up of patients with CKS. We assess available evidences regarding topic, locoregional, and systemic treatments of CKS. We also provide a focus on novel treatment strategies and therapeutic approaches currently under evaluation in clinical trials.

Conclusion: CKS is a rare disease and its management requires a multidisciplinary assessment. Treatment in referral centers and enrolment in clinical trials might impact on outcomes.

Keywords: classic Kaposi's sarcoma, HHV-8, chemotherapy, immunotherapy, anti-PD-1, anti-CTLA-4, guidelines

Introduction

Kaposi sarcoma (KS) is a rare cutaneous neoplasm of endothelial origin. The causative agent is the human herpes virus-8 (HHV-8) which causes cell proliferation, particularly in individuals with compromised immune system.[1] The disease was first described in 1872 by a Hungarian dermatologist, as a pigmented cutaneous sarcoma primarily located on the lower extremities.

Conventionally, four subtypes of Kaposi sarcoma (KS) are described: classic KS (CKS), epidemic KS (HIV-related), endemic (African), and iatrogenic. Recently, a fifth subtype affecting men having sex with men has been added (Table 1). The incidence of CKS is higher in Southern Europe, and in Iceland, reflecting the different seroprevalence of HHV-8 observed in several isolated populations.[2] Despite the improved understanding of CKS's etiology, many aspects of this disease entity remain unclear. High-quality evidence and treatment recommendations for the management of KS are limited to the acquired immune deficiency syndrome (AIDS)-related KS. In contrast, due to the rarity of the disease, there is a lack of consensus regarding the indications for systemic therapy in CKS, and the clinical approach relies on small retrospective case series and experiences of clinicians in few selected institutions.[3,4]

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Table 1 Main Characteristics KS Subtypes

KS Variant	Age at Diagnosis	Geographic Region	Sex Prevalence	Preferred Localizations
Epidemic or AIDS-related	Middle adulthood	n.a.	M	Trunk, head and neck region
Classic or Mediterranean	Elderly	Mediterranean (eg, Italy, Greece) Eastern Europe Middle East	M	Inferior limbs
Endemic or African	Childhood Adulthood	Equatorial Africa	M	Lymph-node (children); inferior limbs (adults)
Iatrogenic or transplant-related	n.a.	n.a.		Trunk, head and neck region
HIV-negative men who have sex with Men	40–60 y.o.	n.a.	M	Inferior limbs

Abbreviations: n.a, not associated; M, male; y.o., years old.

In a systematic review of the literature, Regnier-Rosencher concluded that the evidence for choosing CKS treatment is of low quality and varies among different centers.[5] Due to the chronic course of the disease, treatment goals of CKS extend beyond disease control and include symptoms palliation, prevention of progression, edema reduction, and psychological support.[6]

Over the last few years, a growing interest in the management of CKS has been registered, however with little impact on therapeutic recommendations and no conclusive evidence supporting a specific therapeutic strategy. Therefore, further studies are needed to define the best diagnostic and therapeutic strategy for patients with CKS and to standardize the assessment of disease activity and clinical response during treatment.

CKS diagnostic and treatment difficulty is due to its rarity since KS patients are mainly HIV-positive. Systemic therapy for many years has been represented by chemotherapy but with the affirmation of translational research, it could also count on immunotherapy and target therapies.

In this review, we describe the main mechanisms of KS pathogenesis, the clinical presentation, and recommended diagnostic tools for the clinical assessment of CKS. We also collect available evidences on the management of patients with CKS, including locoregional and systemic treatment. Additionally, we summarize the multidisciplinary team's approach with the aim of providing practical recommendations for the diagnosis and treatment of this rare disease. We also present the most promising future perspectives and the ongoing clinical trials in this field.

Materials and Methods

A search of the literature was conducted using the PubMed/MEDLINE database with search terms including: "Kaposi Sarcoma", "Kaposi treatment", "Kaposi guidelines", "antineoplastic agents", "chemotherapy", "radiotherapy", "electro-chemotherapy". The search was limited to articles in the English language, published between January 1990 and September 2023.

A total of 85 out of 565 articles were selected. Reasons for articles' exclusion were the following: case reports (n = 191); reports on AIDS-related KS only (n = 150); reports on transplant-related KS only (n = 13); overlapping results (n = 32); articles in a language other than English (n = 45); not related to the topic (n = 49) (Figure 1).

Subtypes of Kaposi Sarcoma

Classic Kaposi Sarcoma

CKS typically affects elderly individuals and follows a protracted and usually indolent clinical course. The median age at diagnosis is 70 years, and it is more frequently observed in men of Mediterranean origin, especially Italians, Greeks, and

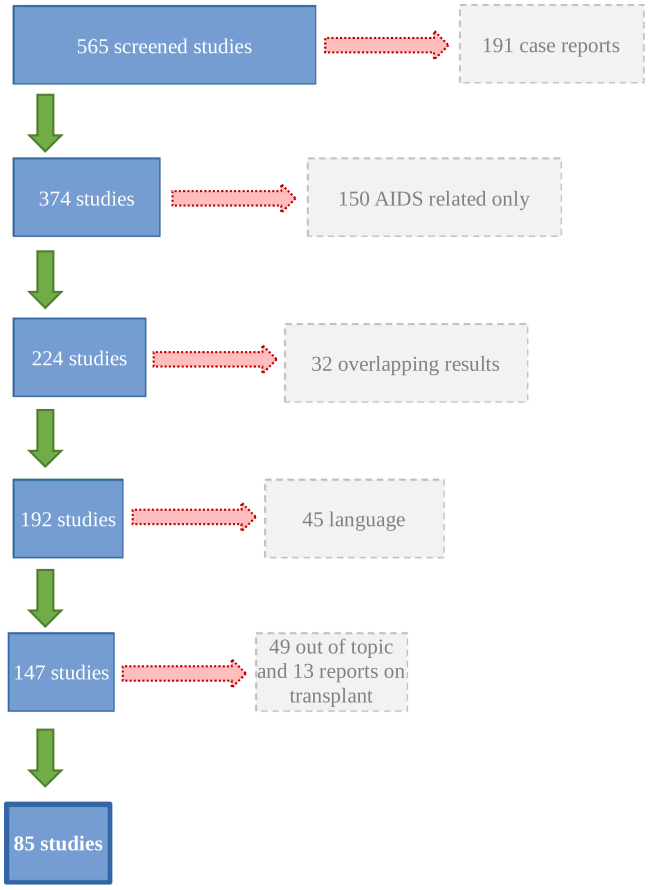

Figure 1 Papers screened in the literature review.

Jews. Lesions associated with CKS are generally slow-growing skin tumors situated on the lower extremities. Visceral involvement is uncommon, occurring in <10% of the cases. However, patients with visceral involvement have a higher risk of developing secondary malignancies. Occasionally aggressive presentation as well as the significant morbidity of CKS can occur with long-term nodal and cutaneous KS. So, CKS commonly causes local invasion than distant spread, and distant metastases occur through the vasculature or lymphatics. The most frequent sites of metastases include the gastrointestinal tract and the lungs, while the bone and upper aerodigestive tract are less often involved.[7,8]

To date, the systemic treatment of CKS primarily relies on cytotoxic chemotherapy, mainly anthracyclines, vinca alkaloids, and paclitaxel, resulting in 70–90% of the transient responses.[9–12] Other effective drugs for CKS include etoposide, gemcitabine, and bleomycin.[9–12] In most cases, CKS is a chronic and relapsing disease requiring multiple systemic treatments over time, thus leading to poor tolerability, increased risk of cumulative toxicities and impaired quality of life.[12]

HIV-Related Kaposi Sarcoma

HIV-related KS was a relatively common and challenging disease during the late 1980s and early 1990s. This is an aggressive disease which often involves viscera, mucosae, and lymph nodes. Involvement of the head and neck region, as well as the trunk, is common. Until a few decades ago, HIV-related KS was associated with considerable morbidity and mortality, with a five-year overall survival (OS) rate of ~12%.[13] The risk of HIV-related KS is higher in homosexual men, and in individuals with untreated AIDS, with a risk that is 500-fold higher than that of the HIV-negative population. Importantly, the reduction of CD4 lymphocytes correlates with more aggressive disease course. With the advent of highly active anti-retroviral therapy (ART), both the incidence and associated mortality from HIV-related KS have significantly declined, with survival rates ranging from 68% to 95%.[13]

Endemic Kaposi Sarcoma

Endemic KS (EKS) is predominantly observed in Sub-Saharan Africa, with a peak prevalence observed through a narrow belt, extending from the Uganda, Sudan, and the Democratic Republic of Congo borders southward through Rwanda and Burundi.[14] EKS typically occurs in two age groups: children (median age: 4–9 years) with an almost one to one sex ratio, and in adults with a high male preponderance.[15] Whilst EKS clinical behavior in adults is generally mild, in children it is usually an aggressive disease characterized by lymphadenopathic presentation, which, in the absence of treatment, can quickly progress to visceral involvement and clinical deterioration.[15]

Iatrogenic Kaposi Sarcoma

Iatrogenic KS typically develops in individuals who underwent induced and prolonged immunosuppression.[16] This immunosuppression can be required for various medical reasons, such as organ transplantation, gastrointestinal inflammatory disease, rheumatologic conditions, or specific chemotherapy regimens. Notably, the prolonged use of high doses of systemic corticosteroids is associated with a higher risk of developing iatrogenic KS. Among organ transplant recipients, there is a 60-fold higher risk of developing KS compared to the general population.[17] Iatrogenic KS usually manifests months to years after initiating an immunosuppressive regimen, and resolves shortly after discontinuation or dose reduction of immunosuppressive agents.

HIV-Negative Men Who Have Sex with Men

A fifth epidemiological form of KS has been recently identified among HIV-negative men who have sex with men (MSM).[18] This KS subtype differs from CKS, as it tends to develop at a younger age and typically presents as a milder form of the disease, not requiring systemic treatment. Among these patients, neither cellular nor humoral immunodeficiency has been reported. These patients are HHV-8 positive, and there is rarely an association with lymphoproliferative disorders, such as Castleman disease, follicular lymphoma, or Burkitt lymphoma.[18]

Pathogenesis

The exact pathophysiology of KS is not fully understood.[18] While HHV-8 infection is recognized as a causative factor, not all individuals infected with HHV8 develop KS.[19] HHV-8, also known as Kaposi sarcoma-associated herpesvirus (KSHV), is a large double-stranded DNA virus belonging to the herpesvirus family. The precise timing and mechanisms of HHV-8 infection are not well defined. The virus expresses a protein called latency-associated nuclear antigen (LANA), which is essential for HHV-8 replication and the modification of host cell expression. HHV-8 induces abnormal lymphangiogenesis, but its spread to visceral organs through the vascular system is uncommon. Indeed, the dissemination is more likely to occur through local extension.[1,20]

Several molecular factors have been investigated for their potential role in KS pathogenesis. The high mobility group box 1 (HMGB1), a DNA ligand involved in several cellular processes, serves as a key regulator of cytokines and growth factors, including CXC Motif Chemokine Ligand 5 (CXCL5), Platelet-Derived Growth Factor-AA human (PDGF-AA), Granulocyte-Colony Stimulating Factors (G-CSF), Extracellular Matrix Metalloproteinase Inducer (EMMPRIN), Interleukin 17A (IL-17A), and Vascular Endothelial Growth Factor (VEGF) in KS.[20] Biomolecular investigation has highlighted the involvement of several molecular pathways, including cell cycle regulators such as p53 and Rb, angiogenesis-related factors (eg, VEGF, angiopoietin family, cyclooxygenase 2, and angiogenin), and extracellular modelling (tumor growth factor [TGF-beta], fibroblast growth factor [FGF2]).[21]

Various factors, including high levels of VEGF and IL-6, chronic exposure to corticosteroids, volcanic soil, iron, aluminosilicate, and clay absorption, have been correlated with the induction of dermal lymphatic alterations contributing to impaired local immunity and predisposing patients to HHV-8 infection.

Table 2 summarizes the major known pathogenic factors associated with the development of KS.

Table 2 Major Pathogenic Factors for the Development of KS

VEGF and angiogenesis	VEGF, IL 6, Cox2
Cytokines and chemokines	Downregulation of TGFb,IFNa and IFNb, Upregulation of IL-1β, TNFα, IL-6, IL-2, IL-4 HMGB1 regulates cytokine and chemokines
Steroids	Modulation of extracellular wall (cadherin). Steroid induced immune suppression (downregulation of GM-CSF); IL-1β, IL-4, IL-5, IL-8, and IL-10; Eotaxin, lipocortin 1 Interaction with NF-κB, activating protein 1, p53, cAMP response element (CRE)-binding protein, STAT-3, STAT-5.
Viral	HHV8; viral miRNAs, miR-K6 and miR-K11
Trauma (Koebner phenomenon)	Injury to the skin can trigger KS
Chronic lymphedema	Lymphangiogenesis
Genes and pathway involved	Inhibition of p53 and pRB and TERT cyclinE/Cdk2 and cyclin A/CdK2; JNK/SAPK, PLC/PKC, MAPK, PI3K/Akt/mTOR, NF-AT and NFκB
Other Immunosuppressant	Anti IL 17 anti IL 23 cyclosporin methotrexate

Abbreviations: VEFG, vascular endothelial growth factor; IL, interleukin; GM-CSF, granulocyte–macrophage colony-stimulating factor; STAT, signal transducer and activators of transcription family members; TGF, tumor growth factor; IFN, interferon; TNF, tumor necrosis factor; TERT, Telomerase Reverse Transcriptase; Cdk, kinases cyclin dependent; JNK, Janus Kinase; SAPK, Stress-activated protein kinases; PLC, Phospholipase C; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; PI3K, Phosphatidyl Inositol 3-Kinase; mTor, mammalian target of rapamycin; NFAT, Nuclear factor of activated T-cells; NFKb, nuclear factor kappa-light-chain-enhancer of activated B cells.

Clinical Presentation, Diagnosis, and Staging

The diagnosis of KS may be suspected in patients with reddish-violaceous macules, nodules, or plaques on their extremities, and less frequently on the genital area, head, or trunk.[22] These skin or mucosal lesions can gradually coalesce, regress, and occasionally lead to hemorrhage or infection. In addition, lymphedema is often noticed in KS patients, likely due to the involvement of lymphatic endothelial cells and lymph nodes, leading to the obstruction of lymphatic outflow. Due to their vast morphologic spectrum, KS lesions often represent a diagnostic challenge, with other skin conditions (eg, hemangioma, pyogenic granuloma, purpura, or bacillary angiomatosis) being difficult to distinguish clinically from KS.

Dermoscopic evaluation generally shows a bluish-red-purple pigmentation, scaly surface, and occasionally the so-called "rainbow pattern" (ie, juxtaposition of multiple colors of the rainbow spectrum). These findings offer a useful, though not specific, tool for the diagnosis of KS.[22] Similarly, Doppler ultrasonography, which reveals a hypoechoic, well-defined lesion with increased vascularity in the inferior part, can be helpful in delineating deep margins of nodular KS lesions and in diagnosing equivocal KS-like lesions. However, the absence of any vascular flow on Doppler-mode among KS patches and plaques limits the usefulness of ultrasonography in this type of lesions.[22]

A biopsy is required to establish the diagnosis, as the presence of spindle-shaped cells interspersed with abnormal vascular channels is a hallmark across different KS subtypes. These cells express endothelial and lymphatic markers on immunohistochemistry (IHC), such as factor VIII-related antigen, CD31, CD34, and D2-40.[23] IHC positive staining for LANA is diagnostic for HHV-8 infection and allows differential diagnosis between KS and other vascular tumors, such as hemangioma or angiosarcoma, in which LANA is absent. Histological variants of KS include: anaplastic, lymphedematous, telangiectatic, hyperkeratotic, micronodular, pyogenic granuloma-like, with ecchymoses, and intravascular KS.[24]

Standard classification for solid tumors, such as the Tumor, Node, Metastasis (TNM), is not useful for KS, as the disease progresses slowly and the majority of KS patients present with skin disease alone. Over the years, various staging systems for KS have been proposed. However, there is still no consensus on the official staging system to use, especially for HIV-negative patients (Tables 3–5). For classic and iatrogenic KS, Brambilla et al proposed a staging system

Table 3 Staging of CKS According to the System Proposed by Brambilla et al

Stage	Prevalent Cutaneous Lesions	Progression in 3 Months of Observation	Visceral Involvement (V)
I Macular-nodular	Macules e/o nodules on the lower limbs	A, slow progression	± V
		B, rapid progression	
II Infiltrative	Plaques on the lower limbs	A, slow progression	± V
		B, rapid progression	
III Florid	Exuberant angiomatous nodules predominantly on the lower limbs	A, slow progression	± V
		B, rapid progression	
IV Disseminate	Angiomatous lesions on the head, trunk and mucosae	A, slow progression	± V
		B, rapid progression	

Notes: Reprinted with permission from Brambilla L, Genovese G, Berti E, et al. Diagnosis and treatment of classic and iatrogenic Kaposi's sarcoma: Italian recommendations. Ital J Dermatol Venerol. 2021;156(3):356–365.[26]

Table 4 The AIDS Clinical Trials Group (ACTG) System for AIDS-Related KS

Tumor (T)	Extent of tumor
T0 (good risk)	Kaposi sarcoma is confined to skin and/or lymph nodes and/or demonstrates minimal oral disease; the Kaposi sarcoma lesions in the mouth are flat rather than raised
T1 (poor risk)	Kaposi sarcoma lesions are widespread; one or more of the following is present: • Edema due to the tumor • Extensive oral Kaposi sarcoma: nodular lesions (raised) and/or lesions in areas of the mouth besides the palate • Lesions of Kaposi sarcoma are in organs other than the lymph nodes (eg, lungs, intestine, and liver)
Immune system (I)	**Status of the immune system, as measured by CD4 cell levels**
I0 (good risk)	CD4 cell count is ≥200/μL (normal range, 600–1500/μL)*
I1 (poor risk)	CD4 cell count is < 200/μL*
Systemic illness (S)	**Extent of involvement within the body or systemic illness**
S0 (good risk)	No systemic illness present; all of the following are true: • No history of opportunistic infections or thrush • None of the following B symptoms is present: unexplained fever, night sweats, >10% involuntary weight loss, diarrhea persisting for >2 weeks • Karnofsky performance status score is ≥70 (ie, patient is up and about most of the time and able to take care of him- or herself)
S1 (poor risk)	Systemic illness present; one or more of the following is true: • History of opportunistic infections or thrush • One or more B symptoms are present • Karnofsky performance status score < 70 • Other HIV-related illness is present (eg, neurologic disease or lymphoma)

Notes: *more recent studies have used counts of either 150 or 100/μL. Adapted with permission from Wolters Kluwer Health, Inc.: Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. *J Clin Oncol.* 1989;7(9):1201–1207. Available from: https://ascopubs.org/doi/10.1200/JCO.1989.7.9.1201?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.[27]

currently used by Italian dermatologists, which is based on the clinical presentation and evolution of the disease (Table 3).[25,26] In contrast, patients with AIDS-related KS are typically staged according to the AIDS Clinical Trials Group (ACTG) staging system, which considers the extent of tumor, immune status, and presence of concomitant

Table 5 System for KS Staging by Schwartz et al

Stage I	Localized nodular KS with >15 cutaneous lesions or involvement restricted to one bilateral anatomic site and few, if any gut nodules
Stage II	Includes both exophytic destructive lesions and locally infiltrative cutaneous lesions as locally aggressive Kaposi sarcoma
Stage III	Generalized lymphadenopatic KS has widespread lymph node involvement with or without skin lesions, but no visceral involvement
Stage IV	Disseminated visceral KS has widespread disease, with multiple visceral organs involvement

Note: Data from Schwartz et al.[28]

systemic illnesses (Table 4).[27] In this classification, limited disease involving localized regions of the skin, lymph nodes, or oral mucosa is staged as T0; the presence of edema and ulceration is considered T1 disease and indicates extensive mucosal and visceral disease. The presence of systemic illness confers a poor prognosis: S1 patients include those with present history of opportunistic infections or thrush; Karnofsky performance status (KPS) <70, or with other HIV-related illness, such as neurological disease or lymphoma. Another proposed staging system for KS is reported in Table 5.[28]

The majority of patients present with cutaneous disease, but KS may also involve the oropharynx, external genitalia, lymph nodes, and visceral organs, mostly the gastrointestinal tract and lungs.[1,29] Therefore, a thorough history, physical examination, and global clinical assessment by a multidisciplinary team are mandatory in order to assess the presence of extracutaneous disease.

Laboratory Tests

All patients with clinically suspected or biopsy-proven KS should be tested for HIV infection, while patients with known HIV should undergo CD4 lymphocyte count and plasma HIV viral load.

HHV-8 serology is useful for confirming KS diagnosis, especially in cases of non-diagnostic tissue biopsy. However, it is worth noting that this test is not routinely performed in many laboratories. Plasma HHV-8 viral load testing could serve as a cost-effective guide to determine which patients should undergo further investigation such as whole-body computed tomography (CT), Positron Emission Tomography (PET) with the radionuclide 18F-fluorodeoxyglucose (FDG), and/or biopsy. This is particularly important to exclude other HHV-8-related disorders, such as multicentric Castleman's disease, and primary effusion lymphoma.[30] For this reason, HHV-8 viral load should be assessed in patients with established KS presenting systemic symptoms such as unexplained fever, weight loss, and lymphadenopathy. Excluding these cases, HHV-8 viral load testing is rarely recommended due to minimal variations over time and the lack of a significant association between HHV-8 viral loads and the intensity of virus-specific cellular immunity.[31]

Additionally, KS patients should undergo a complete blood count test, serum protein electrophoresis, inflammatory markers (C-Reactive Protein [CRP], and erythrocyte sedimentation rate [ESR]), and fecal occult blood testing (preferably three samples) to rule out concomitant gastrointestinal involvement.

Endoscopy and Imaging Studies

Newly diagnosed KS patients should undergo endoscopy and imaging studies for possible extra-cutaneous involvement. These procedures include esophagogastroduodenoscopy and otorhinolaryngological assessment including flexible endoscopy, chest X-ray, and complete abdominal ultrasound. Patients with a positive fecal occult blood test or clinical lymphadenopathy should also undergo colonoscopy and lymph node ultrasound scans, respectively.

A whole-body CT scan should be preferred over the above-mentioned procedures in cases of aggressive and/or AIDS-related disease to provide a more accurate assessment of lymph nodes, viscera, or bones, as liver involvement is common.[32] Except for these cases, extensive contrast-enhanced imaging studies are not routinely required.[33] It is important to note that endoscopy remains the gold standard for diagnosing gastrointestinal lesions, as they are often small and submucosal, thus difficult to detect with other methods.[34]

Magnetic resonance imaging (MRI) allows for a more detailed evaluation of locally aggressive KS with soft-tissue and skeletal involvement, avoiding radiation exposure.[35,36] 18-FDG PET is known to avidly accumulate in certain tumors, but its utility in KS remains unclear.[33] On the other hand, 18-FDG PET combined with CT (18F-FDG-PET/CT scan) can be useful for whole-body staging and disease response assessment during treatment.[32,34]

Follow Up

Patients with indolent disease, such as the majority of patients with CKS, HIV-positive receiving ART, or those with iatrogenic KS following a reduction in immunosuppressant regimens, should not undergo extensive radiologic assessment during follow-up.[26] These patients should be followed up with complete blood count, fecal occult blood testing, and a dermatological assessment, every 6 months or yearly. Assessing the response to systemic treatment can be challenging in patients with extensively spread cutaneous lesions. Clinicians treating patients with KS of the skin or visible mucosae may utilize digital photography to create a record and assess the disease's progression and the effects of therapeutic approaches.

Conversely, patients experiencing acute worsening of KS should undergo additional diagnostic procedures, including esophagogastroduodenoscopy, colonoscopy, abdominal and lymph node ultrasound, or CT scan, to investigate potential visceral involvement. The choice of the type of procedure should be based on the patient's history, physical examination, and laboratory testing.

Although NCCN guidelines do not support the use of node ultrasound and fecal occult blood testing, we recommend in our tertiary center based on the fact that they are not expensive neither invasive tests. Evaluation of visceral disease is not required in patients with HIV-associated KS, but we perform ultrasound scan during the routine dermo-oncologic visit.[26]

Therapeutic Approach

Treatment depends on the severity and extent of the disease, patient's characteristics, and comorbidities. Ideally, the therapeutic strategy should be guided by a multidisciplinary team including dermatologists, oncologists, radiation oncologists, and infectious disease specialists, depending on the extension of the disease and its etiology. The majority of patients with CKS might benefit from local therapies only, while systemic therapy is required for symptomatic and/or rapidly progressing disease. Local therapy mainly consists of intralesional chemotherapy administration, radiotherapy, and electrochemotherapy. Compression stockings are often used in patients with lesions on the lower limb lesions to treat edema, which can severely impact the quality of life.[37] By improving edema, compression stockings help reduce lesions, changing them from plaques and nodules to macules, and consequently reducing limb volume, as reported in our previous case series.[37]

Beyond local approaches, there is currently no clear consensus on the appropriate timing for initiating systemic treatment. In a multivariate analysis on 160 patients, the following risk factors that might indicate systemic therapy initiation were identified: time between first symptoms and diagnosis ≥1 year, endemic KS, total number of lesions ≥10, visceral involvement, head or neck localization, and presence of edema.[38] So far, systemic treatment mostly consists of single-agent chemotherapy with cytotoxic drugs. Although various experimental agents have been studied in recent years (eg, antiangiogenic drugs and immunotherapy), none of them has yet been approved as the standard systemic treatment.[7]

Topical Therapy

Local therapy is generally indicated for the treatment of localized KS with mild disease, or when systemic therapy is not feasible, usually related to patients' conditions. Indeed, even if systemic treatment in KS is low-dose chemotherapy, which has very few side effects, it requires numerous hospital visits and as all i.v. hospital administration is not indicated for ECOG Performance Status 3 or more. Noteworthy nor older age neither cardiologic or nephrological comorbidity might lead clinicians to withhold these important therapies. In most cases, intralesional treatment is more appropriate, as it delivers a higher drug amount at the tumor site with a more manageable safety profile. According to a recent systematic review based on case reports/series and a few clinical trials, the three most commonly used topical agents to treat cutaneous KS are alitretinoin, imiquimod, and timolol, all of which have demonstrated clinical efficacy with minimal drug-related adverse events.[39–44] Notably, alitretinoin is the only FDA-approved topical medication for KS, with a labeled indication for AIDS-related cutaneous KS. However, its efficacy in treating KS appears limited, as only 36.1% of patients experience a complete (CR) or partial response (PR) after many weeks of treatment.[39]

Topical imiquimod and timolol also require several applications over weeks/months, and their penetration into the skin may be poor, especially on the lower limbs. However, they may be useful in patients with mucosal lesions or in combination with other local treatments. For example, a combination of cryotherapy and topical imiquimod (3 times a week for 2 months) lead to a complete resolution of lesions in 89% of patients. Side effects included pain during cryotherapy, occasional blister formation (which may lead to scarring), and mild inflammation due to imiquimod.[42]

There are also reports of less widely used topical treatments, such as silver nitrate cauterization and nicotine patches, which have shown variable clinical efficacy for cutaneous KS.[45,46] Notably, a reduction of ≥50% in the extension of KS lesions was achieved in 25% of cases with the use of nicotine patches.[46]

Intralesional Therapy

Intralesional injection of vincristine is a rapidly effective, painless, and cost-effective treatment which can be used for a significant number of lesions even in the same session. The overall response rate reported is 94.6% after a single injection of vincristine.[47] Vinblastine and bleomycin can also be used for intralesional injections. However, there are fewer related studies, and bleomycin is associated with a higher incidence of pain at the injection site compared to vincristine.[48]

Some case series in the 1990s have reported a decrease of ≥50% in an average of 70% KS lesions treated with intralesional IFN alfa-2.[5,49] This treatment generally requires two injections weekly for several weeks and induces important histopathological changes in treated lesions, with a strong correlation with prolonged disease response.[49–52] The clinical response of lesions treated with topical IFN alfa-2 therapy includes a reduction in thickness, size, and consistency.[51]

Two case series evaluated the efficacy and safety of Neodymium:YAG (Nd:YAG) laser in patients with CKS and EKS, with exclusively cutaneous localization, reporting a rapid clinical improvement in up to 80% of the treated patients.[53] More impressive results were observed in HIV-positive patients, particularly in terms of reducing lesion size and flattening elevated lesions.[54]

Given the lack of standardized clinical guidelines for cutaneous KS topical and intralesional therapy, further randomized controlled trials are needed to more accurately assess clinical outcomes, treatment regimens, and adverse effects associated with these agents.

Electrochemotherapy

Electrochemotherapy (ECT) is a local approach used for cutaneous metastatic nodules and primary skin tumors, such as melanoma. ECT combines the delivery of short and intense electrical pulses (electroporation), with the administration of non-permeant or poorly permeant anti-cancer drugs (eg, bleomycin and cisplatin).[55,56] In patients with cutaneous CKS lesions, ECT demonstrated a significant effect on HHV-8 kinetics, with complete disease remission observed in patients with complete clearance of circulating virus.[57]

In a prospective non-randomized Phase II trial of ECT in patients with KS, disease response was reported in all treated patients (n = 23), with CR in 61% and PR in 39%, respectively. Treatment was well tolerated, with an improvement in quality of life reported in 95% of patients.[57] A prospective series of 19 patients undergoing ECT reported a CR rate of 73.6%, with 5 out of 19 patients requiring a second (15.7%) and third (10.5%) course of ECT.[58] Similar results were reported in a prospective trial of 376 patients with cutaneous tumors, including 41 patients with KS.[59]

A retrospective series of patients with cutaneous tumors, including KS, treated with a reduced bleomycin dosage, showed a similar therapeutic effect to the standard chemotherapy dose, suggesting a potential application in patients with impaired renal function or candidate to multiple ECT cycles.[60] The primary limitation of ECT in KS patients is the requirement for sedation, which may be contraindicated in elderly patients, and those with comorbidities. Furthermore, ECT is not a standardized treatment for KS lesions, and may result in significant local adverse effects, including burns, prolonged pain, ulceration, or contracture scars.[61]

Radiotherapy

KS has historically been considered a radiosensitive tumor. Indeed, radiotherapy (RT) provides effective palliation of symptoms, such as pain relief, bleeding control, or edema reduction, for the majority of treated patients.[62,63] In

specialized centers, RT has been reported to be highly effective with long-lasting complete responses in approximately 90% of cutaneous and mucosal lesions.[64,65]

Hence, RT can be useful in selected cases of locally aggressive cutaneous KS. However, high doses should be approached with caution because of possible acute and long-term adverse effects including erythema, edema, and ulceration, particularly in the setting of coexisting lymphedema. Months or years after RT, signs of chronic radiodermatitis can occur, including skin atrophy, telangiectasia, hyper- or hypopigmentation, and ulceration.[66] RT-related toxicity can be mitigated by using lower-dose RT regimens and avoiding irradiation of healthy skin, as suggested by most retrospective case series reporting low rate of adverse events.[67] Caution should be used in case of irradiation of sites of pre-existing lymphedema. Similarly, KS lesions that continue to progress despite radiation are unlikely to respond to repeated RT (50% show partial regression, and 50% show progressive disease); therefore, re-irradiation should be considered only in selected cases.[68] In cases of advanced cutaneous KS, radiation should be reserved for situations where systemic therapy is not feasible and is used as palliative therapy.

Various RT dosing schemes may be used from 15 to 30 Gy depending on extension: lower doses are preferred for smaller and more superficial lesions, while higher doses may be used for more extensive, deeply invasive lesions.[69] In a retrospective series of more than 1700 KS lesions treated with RT, the most commonly prescribed RT doses ranged from 10 to 40 Gy in patients with CKS, and between 5 and 45 Gy in patients with HIV-related KS.[64] In the latter population, the lowest doses (5–15 Gy) were administered to small (0.5–1 cm) macular lesions often localized on the face and oral mucosa; the intermediate doses (20–30 Gy) were administered to most papular and nodular lesions; and the highest (35–45 Gy) were administered to a few infiltrated and resistant lesions. In a prospective randomized trial of patients with EKS, the use of hypofractionated regimens produced equivalent results in terms of treatment response, local recurrence-free survival, and toxicity, as compared with conventional fractionation regimens.[65] In a prospective randomized trial of patients with EKS, the use of hypofractionated regimens produced equivalent results in terms of treatment response, local recurrence-free survival, and toxicity, as compared with conventional fractionation regimens.[70] However, more fractionated regimens may be preferred for sites with adjacent radiosensitive structures, such as the oral cavity.

Systemic Treatment

In all KS subtypes, optimization of immune function and avoidance of further immunosuppression are critical to prevent additional KS lesions, and maintain disease response.

As mentioned before, standardized recommendations for the choice of systemic treatment are available only for AIDS-related KS.[71] In this specific setting, the reconstitution of immune function through ART and the maintenance of viral suppression are the mainstays of KS treatment. In fact, by treating the HIV infection, the immune system is enabled to defend itself against opportunistic infections, including HHV-8. Paradoxically, some patients will respond to the initiation of ART with KS progression, a transient phenomenon called Kaposi sarcoma immune reconstitution syndrome (IRIS). In patients with AIDS-related KS, the preferred first-line systemic therapy for both limited cutaneous disease and advanced disease is liposomal doxorubicin. An alternative option for first-line systemic therapy for limited cutaneous and advanced disease is paclitaxel.[71] In a randomized trial comparing pegylated liposomal doxorubicin and paclitaxel, both regimens appeared to be active in advanced, symptomatic disease, but with a higher rate of high-grade treatment-related toxicity for paclitaxel.[72] A systematic review of randomized trials and observational studies in patients with advanced AIDS-related KS found no significant differences between liposomal doxorubicin, liposomal daunorubicin, and paclitaxel, although the number of identified studies was limited.[73]

Recommendations for first-line systemic therapy for CKS are mostly based on smaller case series, since there are no randomized clinical trials in this setting. Several chemotherapy agents have been evaluated for the treatment of CKS.

The French dermo-oncology group led a multicentre retrospective study (110 patients, 62.7% CKS and 37.2% EKS) comparing the effectiveness and safety of the main recommended systemic therapies, namely liposomal doxorubicin, paclitaxel, and low-dose interferon. The authors confirmed systemic localization and ulcerated lesions at diagnosis as negative prognostic factors. Among the therapies, they concluded that either liposomal doxorubicin or paclitaxel and, to a lesser extent, interferon are safe and effective treatments for non-immunodeficient KS. The good ORR emphasizes the need to compare new and expensive treatment options (anti PD-1) with these standard systemic approaches.[74]

In a retrospective study on 44 CKS patients treated with weekly paclitaxel, Paksoy et al reported a disease control rate of 79.6% (with 15.9% of patients experiencing CR), and a median progression-free survival (PFS) of 35.1 months.[12] Our group reported similar results in a cohort of 58 CKS patients, with 94.6% patients achieving a partial or complete response after an average of 13.5 infusions. Duration of response was ≥ 19 months in 58.5%, and < 14 months in 41.5% of patients, respectively. Interestingly, all patients interrupting treatment and subsequently experiencing disease relapse, obtained a complete or partial response upon paclitaxel resumption.[9]

In the 1980–90s popular schedules included combinations of vinca alkaloids, bleomycin (a glycopeptide antibiotic), and anthracyclines. These protocols were used in low-income countries until few years ago such as vincristine/vinblastine alone or in combination with bleomycin were commonly prescribed due to their lower cost and wider availability. Oral etoposide was another choice, given its easy access in an outpatient setting.[1] A study conducted on AIDS-associated KS evaluating paclitaxel or pegylated liposomal anthracycline (PLD) cost-effectiveness compared with etoposide or bleomycin-vincristine in Kenya demonstrated bleomycin-vincristine would be cost-effective compared with etoposide, and paclitaxel would be cost-effective compared with bleomycin-vincristine, while PLD would not be cost-effective compared with paclitaxel.[75] Another therapeutic option, still used in Italy, is intravenous gemcitabine, which showed high disease control rates with prolonged clinical benefit in retrospective studies.[76,77]

In patients experiencing disease relapse after first-line, the same systemic options can be considered in further lines if previous treatment was well tolerated, provided disease response lasted at least 3 months. For patients with AIDS-related KS, following treatment with liposomal doxorubicin and paclitaxel, treatment with pomalidomide is recommended.[71] Pomalidomide is an oral immunomodulator, derivative of thalidomide, active both in KS with or without HIV. It targets cereblon, an E3 ligase, and modulates TNF alpha, IL-6 and VEGF, leading to T-cell and NK cell activation (studies demonstrate ORR ranges 51–87%, with manageable haematologic toxicities and satisfactory PFS).[74,78]

Alternative options for subsequent lines of therapy for relapsed/refractory disease include bortezomib, gemcitabine, lenalidomide, and vinorelbine.

In Italy, first line PLD and taxanes are widely used, pomalidomide is not approved by the Italian Medicines Agency, second line options include enrollment in clinical trial or vinblastine/bleomycin or etoposide. Table 6 summarizes the main therapeutic options and corresponding treatment schedules for CKS. Patients can continue through all treatment options

Table 6 Systemic Therapy for CKS

First line treatments	Agent	Dosage
	Paclitaxel	100 mg (fixed dose) IV qw; 60–100 mg/m2 IV qw or q2w
	Liposomal doxorubicin	20 mg/m2 IV q2w or q3w
	Vinblastine + Bleomycin	Vinblastine (induction 4, 6, 8 mg I.V. weekly) 10 mg IV + Bleomycin 15 IU IM q3w
Second line treatments	Etoposide	50–150 mg/day PO for 7 days of each 14-day cycle
	Vinblastine	10 mg IV q2w or q3w
	Gemcitabine	1.2 g IV qw
	Vinorelbine	20 mg/m2 q2w
	Pomalidomide	5mg PO daily days 1–21 q4w
Third line treatments	Pembrolizumab	200 mg IV q3w
	Imatinib	400 mg/day PO
	Ipilimumab + Nivolumab	Ipilimumab 1 mg/kg IV q6w and Nivolumab 240 mg IV q2w

Abbreviations: IV, intravenous; PO, orally, qw, every week.

listed, and considering the cumulative toxicity of certain chemotherapy treatments can be repeated if they were tolerated and the response was durable.[71] In selected cases, the best supportive care may be an appropriate option.

In our centre, systemic treatment is selected by the multidisciplinary team, considering disease extension and biologic behaviour, performance status, comorbidities, and patient's preferences. As an example, taxane or bleomycin-based combinations are the preferred choice in case of fast-progressing and aggressive disease.

A pilot study of bevacizumab and doxorubicin in two cohorts, HIV negative and HIV positive on ART patients, demonstrated promising outcome (ORR 56% and PFS 6,9 months) and few but severe adverse events (35% G3-4).[79]

Although only 16 patients were evaluated, the VEGF value reduced significantly with the combination but the benefit of adding anti-VEGF considering the side effects needs further investigation.[79]

Future Perspectives

The recognition of viral genes by host cells initiates DNA damage response, which may increase genetic instability and oncogenic alterations, rendering viral-induced cancers a potential target for immunotherapy. Based on the evidence of PD-1/PD-L1 blockade efficacy in virus-induced tumors, such as Merkel cell carcinoma, over the last years immune-checkpoint inhibitors (ICIs) have been investigated also in patients with CKS, showing promising results.[80,81] In 2022, the results of a phase II trial led to the phase transition success rate (PTSR) indication benchmark for progressing into Food and Drug Administration (FDA) approval of pembrolizumab for the treatment of classic and endemic KS in the United States (US).[81] In this trial, 17 patients (eight [47%] with classic and nine [53%] with EKS) received pembrolizumab for 6 months, or until severe toxicity occurred. Fourteen patients had received previous systemic treatment in first line: 3 (18%) patients received first-line IFN, and 11 (65%) chemotherapy. After a median follow-up of 20.4 months, 12% of patients had a CR, 59% had a PR, and 29% had stable disease (SD), with a best overall response rate of 71%. Among the responders, the median time to response was 4.8 months and, in a post-hoc analysis, the estimated median duration of response was 23.4 months. The median time to progression was 24 months: 12 patients had a time to progression > 12 months, and 2 patients > 24 months. Safety profile was consistent with data from previous trials, and there were no treatment-related deaths.[81]

The combination of ipilimumab and nivolumab was evaluated in a phase II study in 18 chemo-refractory patients with CKS. Treatment consisted of nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks and was continued for up to 24 months or until either withdrawal of consent, intolerable toxicity, or disease progression. At a median follow-up of 24.4 months, the overall response rate by RECIST v1.1 was 87%. The 6-month and 12-month PFS rate was 76.5% and 58.8%, respectively. Only four patients (22%) experienced grade 3–4 adverse events.[82] Interestingly, biomarkers of ICIs response, such as PD-L1 expression in tumor cells, TMB, and tumor-infiltrating lymphocytes (TILs), were low or negative in most patients, regardless of treatment response. Marked overexpression of immune-related genes and immunotherapy targets was observed, such as *4–1BB, CTLA4, CD40, CD27, OX40, GITR, LAG3, TIM3, PD-1*, and *PD-L1 (CD274)* gene, suggesting there might be a post-transcriptional regulation of expression associated with benefit from immune checkpoint blockade.[82]

To date, ICIs are not approved as treatment strategy for patients with CKS in Italy.

Despite the relative chemosensitivity of KS, the duration of response is limited which, combined with the chronic course of this disease, might represent a major hurdle. A substantial unmet need exists for a systemic treatment that will provide disease control for a prolonged period of time, without having a major impact on tolerability and quality of life. Several combination strategies are currently under investigation in ongoing clinical trials (Table 7): dostarlimab in combination with ART in refractory HIV-associated KS (NCT05646082); nivolumab and pomalidomide in patients with KS, with or without HIV coinfection (NCT04902443); nivolumab and cabozantinib in patients with HIV-associated KS (NCT04514484). A phase II single-arm trial with pembrolizumab in association with lenvatinib for patients with pretreated chemo-resistant CKS is currently ongoing at our Institution and will soon start recruiting patients (EudraCT number: 2020-004426-36).

Table 7 Clinical Trials on Going

Study	Drugs	Phase	State	Primary Objectives
NCT05846724 PULSAR	Pembrolizumab plus Lenvatinib	II	Not recruiting	ORR
NCT02659930	Pomalidomide+Doxorubicin	II	Recruiting	Safety
NCT04065152 KAPVEC	TVEC Talimogene Laherparepvec	II	Recruiting	ORR OS
NCT04303117	NHS-IL12+M7824	I/II	Recruiting	Safety
NCT03993106	sEphB4-HSA	I/II	Recruiting	Safety
NCT04941274	Abemaciclib	I/II	Recruiting	Safety ORR
NCT05797662	Propranolol	II	Recruiting	Safety ORR
NCT04305691	Ixazomib	II	Recruiting	ORR
NCT04893018	NT-I7	II	Not recruiting	ORR DoR
NCT06052618	Pacritinib	II	Not recruiting	ORR DoR
NCT04902443	Nivolumab+Pomalidomide	II	Recruiting	Safety

Abbreviations: ORR, overall response rate; DoR, duration of response.

Conclusions

KS is a multifaceted and challenging disease, which requires a multidisciplinary approach for diagnosis, staging, and treatment. Due to the chronic course of HHV-8 infection, most patients require periodical assessment after initial diagnosis, with potential need for systemic treatment. The best sequence of treatment is still not known, and several clinical parameters should guide treatment's decision. Quality of life and long-term treatment-related sequelae are of concerns, given the chronic course of the disease together with age and frailty of the majority of patients. Referral to experienced Centers optimizes patients' management throughout the disease. Thorough data collection, together with the results of ongoing clinical trials, will improve the knowledge of KS with potential improvement of disease control rates and survival outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Conceptualization, N.D and A.I.; methodology, A.T.; validation, L.B., O.G., and A.V.M.; formal analysis, N.D. and O.G resources, N.D. and A.I.; data curation, N.D., and A.I.; writing—original draft preparation, N.D., A.I. and A.T.; writing—review and editing, A.V.M. A. T and L.B.; visualization, O.G.; supervision, A.V.M. and O.G.; funding acquisition, O.G. All authors have read and agreed to the published version of the manuscript.

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References

1. Vangipuram R, Tyring SK. Epidemiology of Kaposi sarcoma: review and description of the non-epidemic variant. *Int J Dermatol*. 2019;58:538–542.
2. Stiller CA, Trama A, Brewster DH, et al. Descriptive epidemiology of Kaposi sarcoma in Europe. Report from the RARECARE project. *Cancer Epidemiol*. 2014;38:670–678. doi:10.1016/j.canep.2014.09.009
3. Hengge UR, Esser S, Rudel HP, Goos M. Long-term chemotherapy of HIV-associated Kaposi's sarcoma with liposomal doxorubicin. *Eur J Cancer*. 2001;37:878–883. doi:10.1016/S0959-8049(01)00053-3
4. Uldrick TS, Wyvill KM, Kumar P, et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. *J Clin Oncol*. 2012;30:1476–1483. doi:10.1200/JCO.2011.39.6853
5. Régnier-Rosencher E, Guillot B, Dupin N. Treatments for classic Kaposi sarcoma: a systematic review of the literature. *J Am Acad Dermatol*. 2013;68(2):313–331. doi:10.1016/j.jaad.2012.04.018
6. Radu O, Pantanowitz L. Kaposi sarcoma. *Arch Pathol Lab Med*. 2013;137(2):289–294. PMID: 23368874. doi:10.5858/arpa.2012-0101-RS
7. Cesarman E, Damania B, Krown SE, et al. Kaposi Sarcoma. *Nat Rev Dis Primers*. 2019;5:9. doi:10.1038/s41572-019-0060-9
8. Goff CB, Dasanu CA. Changing therapeutic landscape in advanced Kaposi sarcoma: current state and future directions. *J Oncol Pharm Pract*. 2023;29(4):917–926. doi:10.1177/10781552221148417
9. Tourlaki A, Germiniasi F, Rossi LC, et al. Paclitaxel as first- or second-line treatment for HIV-negative Kaposi's sarcoma: a retrospective study of 58 patients. *J Dermatol Treat*. 2020;31:183–185. doi:10.1080/09546634.2019.1590520
10. Brambilla L, Recalcati S, Tourlaki A. Vinorelbine therapy in classic Kaposi's sarcoma: a retrospective study of 20 patients. *Eur J Dermatol*. 2015;25:535–538. doi:10.1684/ejd.2015.2659
11. Fardet L, Stoebner PE, Bachelez H, et al. Treatment with taxanes of refractory or life-threatening Kaposi sarcoma not associated with human immunodeficiency virus infection. *Cancer*. 2006;106:1785–1789. doi:10.1002/cncr.21791
12. Paksoy N, Khanmammadov N, Doğan İ, et al. Weekly paclitaxel treatment in the first-line therapy of classic Kaposi sarcoma: a real-life study. *Medicine*. 2023;102(5):e32866. doi:10.1097/MD.0000000000032866
13. Lodi S, Guiguet M, Costagliola D, et al. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. *J Natl Cancer Inst*. 2010;102(11):784–792. doi:10.1093/jnci/djq134
14. Simonart T. Role of environmental factors in the pathogenesis of classic and African-endemic Kaposi sarcoma. *Cancer Lett*. 2006;244:1–7. doi:10.1016/j.canlet.2006.02.005
15. Zeinaty PE, Lebbé C, Delyon J. Endemic Kaposi's Sarcoma. *Cancers*. 2023;15(3):872. doi:10.3390/cancers15030872
16. Cahoon EK, Linet MS, Clarke CA, et al. Risk of Kaposi sarcoma after solid organ transplantation in the United States. *Int J Cancer*. 2018;143:2741–2748. doi:10.1002/ijc.31735
17. Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011;306:1891–1901. doi:10.1001/jama.2011.1592
18. Denis D, Seta V, Regnier-Rosencher E, et al. A fifth subtype of Kaposi's sarcoma, classic Kaposi's sarcoma in men who have sex with men: a cohort study in Paris. *J Eur Acad Dermatol Venereol*. 2018;32(8):1377–1384. doi:10.1111/jdv.14831
19. Douglas JL, Gustin JK, Moses AV, et al. Kaposi sarcoma pathogenesis: a triad of viral infection, oncogenesis and chronic inflammation. *Transl Biomed*. 2010;1(2):172.
20. Lipps C, Badar M, Butueva M, et al. Proliferation status defines functional properties of endothelial cells. *Cell Mol Life Sci*. 2017;74(7):1319–1333. doi:10.1007/s00018-016-2417-5
21. Samaniego F, Young D, Grimes C, et al. Vascular endothelial growth factor and Kaposi's sarcoma cells in human skin grafts. *Cell Growth Differ*. 2002;13(8):387–395.
22. Tourlaki A, Nazzaro G, Wei Y, et al. Clinical, dermoscopic, ultrasonographic, and histopathologic correlations in Kaposi's sarcoma lesions and their differential diagnoses: a single-center prospective study. *J Clin Med*. 2022;12(1):278. doi:10.3390/jcm12010278
23. Pantanowitz L, Otis CN, Dezube BJ. Immunohistochemistry in Kaposi's sarcoma. *Clin Exp Dermatol*. 2010;35(1):68–72. doi:10.1111/j.1365-2230.2009.03707.x
24. Grayson W, Pantanowitz L. Histological variants of cutaneous Kaposi sarcoma. *Diagn Pathol*. 2008;3:31. doi:10.1186/1746-1596-3-31
25. Brambilla L, Boneschi V, Taglioni M, Ferrucci S. Staging of classic Kaposi's sarcoma: a useful tool for therapeutic choices. *Eur J Dermatol*. 2003;13(1):83–86. PMID: 12609790.
26. Brambilla L, Genovese G, Berti E, et al. Diagnosis and treatment of classic and iatrogenic Kaposi's sarcoma: Italian recommendations. *Ital J Dermatol Venerol*. 2021;156(3):356–365. doi:10.23736/S2784-8671.20.06703-6
27. Krown SE, Metroka C, Wernz JC. Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria. AIDS Clinical Trials Group Oncology Committee. *J Clin Oncol*. 1989;7(9):1201–1207. doi:10.1200/JCO.1989.7.9.1201
28. Schwartz RA, Micali G, Nasca MR, Scuderi L. Kaposi sarcoma: a continuing conundrum. *J Am Acad Dermatol*. 2008;59(2):179–206. doi:10.1016/j.jaad.2008.05.001
29. Port JH, Traube J, Winans CS. The visceral manifestations of Kaposi's sarcoma. *Gastrointest Endosc*. 1982;28(3):179–181. doi:10.1016/S0016-5107(82)73047-0
30. Haq IU, Dalla Pria A, Papanastasopoulos P, et al. The clinical application of plasma Kaposi sarcoma herpesvirus viral load as a tumour biomarker: results from 704 patients. *HIV Med*. 2016;17(1):56–61. doi:10.1111/hiv.12273
31. Bihl F, Mosam A, Henry LN, et al. Kaposi's sarcoma-associated herpesvirus-specific immune reconstitution and antiviral effect of combined HAART/chemotherapy in HIV clade C-infected individuals with Kaposi's sarcoma. *AIDS*. 2007;21(10):1245–1252. doi:10.1097/QAD.0b013e328182df03
32. Addula D, Das CJ, Kundra V. Imaging of Kaposi sarcoma. *Abdom Radiol*. 2021;46(11):5297–5306. doi:10.1007/s00261-021-03205-6
33. O'Mahony D, Gandjbakche A, Hassan M, et al. Imaging techniques for Kaposi's sarcoma. *J HIV Ther*. 2008;13(3):65–71.
34. Pesqué L, Delyon J, Lheure C, et al. Yield of FDG PET/CT for defining the extent of disease in patients with Kaposi sarcoma. *Cancers*. 2022;14(9):2189. doi:10.3390/cancers14092189

35. Sharma S, Kurra C, Hyska-Campbell M, et al. Kaposi sarcoma mimicking pedal osteomyelitis in a patient with HIV. *Radiol Case Rep*. 2019;14(12):1495–1499. doi:10.1016/j.radcr.2019.09.025
36. Verdecia J, Warda F, Rechcigl K, et al. Kaposi sarcoma with musculoskeletal manifestations in a well-controlled HIV patient. *IDCases*. 2019;17:e00571. doi:10.1016/j.idcr.2019.e00571
37. Brambilla L, Tourlaki A, Ferrucci S, et al. Treatment of classic Kaposi's sarcoma-associated lymphedema with elastic stockings. *J Dermatol*. 2006;33(7):451–456. doi:10.1111/j.1346-8138.2006.00108.x
38. Benajiba L, Lambert J, La Selva R, et al. Systemic treatment initiation in classical and endemic Kaposi's sarcoma: risk factors and global multi-state modelling in a monocentric cohort study. *Cancers*. 2021;13(11):2519. doi:10.3390/cancers13112519
39. Htet KZ, Waul MA, Leslie KS. Topical treatments for Kaposi sarcoma: a systematic review. *Skin Health Dis*. 2022;2(2):e107. doi:10.1002/ski2.107
40. Odyakmaz Demirsoy E, Bayramgürler D, Çağlayan Ç, et al. Imiquimod 5% Cream Versus Cryotherapy in Classic Kaposi Sarcoma. *J Cutan Med Surg*. 2019;23(5):488–495. doi:10.1177/1203475419847954
41. Goiriz R, Ríos-Buceta L, De Arriba AG, et al. Treatment of classic Kaposi's sarcoma with topical imiquimod. *Dermatol Surg*. 2009;35(1):147–149.
42. Abdelmaksoud A, Filoni A, Giudice G, Vestita M. Classic and HIV-related Kaposi sarcoma treated with 0.1% topical timolol gel. *J Am Acad Dermatol*. 2017;76(1):153–155. doi:10.1016/j.jaad.2016.08.041
43. Gu L, Lin E, Liu S, et al. Efficacy of immunotherapy with combination of cryotherapy and topical imiquimod for treatment of Kaposi sarcoma. *J Med Virol*. 2023;95(1):e28396. doi:10.1002/jmv.28396
44. Bernardini B, Faggion D, Calabró L, Oro E, Alaibac M. Imiquimod for the treatment of classical Kaposi's sarcoma. *Acta Derm Venereol*. 2010;90:417–418. doi:10.2340/00015555-0850
45. Brambilla L, Tourlaki A. Silver nitrate for Kaposi's sarcoma nodules: a new look at an old treatment. *J Dermatol Treat*. 2017;28(2):152–154. doi:10.1080/09546634.2016.1214233
46. Goedert JJ, Scoppio BM, Pfeiffer R, et al. Treatment of classic Kaposi sarcoma with a nicotine dermal patch: a phase II clinical trial. *J Eur Acad Dermatol Venereol*. 2008;22(9):1101–1109. doi:10.1111/j.1468-3083.2008.02720.x
47. Brambilla L, Bellinvia M, Tourlaki A, et al. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. *Br J Dermatol*. 2010;162(4):854–859. doi:10.1111/j.1365-2133.2009.09601.x
48. Vassallo C, Carugno A, Derlino F, et al. Intralesional vinblastine injections for treatment of classic Kaposi sarcoma in diabetic patients. *Cutis*. 2015;95(5):E28–34. PMID: 26057517.
49. Trattner A, Reizis Z, David M, et al. The therapeutic effect of intralesional interferon in classical Kaposi's sarcoma. *Br J Dermatol*. 1993;129(5):590–593. doi:10.1111/j.1365-2133.1993.tb00490.x
50. Ghyka G, Alecu M, Halalau F, Coman G. Intralesional human leukocyte interferon treatment alone or associated with IL-2 in non-AIDS related Kaposi's sarcoma. *J Dermatol*. 1992;19(1):35–39. doi:10.1111/j.1346-8138.1992.tb03176.x
51. Alecu M, Ghyka G, Hălălău F, et al. Intralesional human leukocyte interferon treatment in the non-AIDS related Kaposi's sarcoma. *Med Interne*. 1990;28(1):61–67.
52. Tur E, Brenner S. Classic Kaposi's sarcoma: low-dose interferon alfa treatment. *Dermatology*. 1998;197(1):37–42. doi:10.1159/000017973
53. Özdemir M, Balevi A. Successful treatment of classic Kaposi sarcoma with long-pulse neodymium-doped yttrium aluminum garnet laser: a preliminary study. *Dermatol Surg*. 2017;43(3):366–370. doi:10.1097/DSS.0000000000000973
54. Silvestri M, Latini A, Lesnoni La Parola I, et al. Effectiveness and safety of treatment with neodymium:YAG laser 1064 nm in patients with classic and epidemic Kaposi sarcoma. *Bioengineering*. 2022;9(3):106. doi:10.3390/bioengineering9030106
55. Giardino R, Fini M, Bonazzi V, et al. Electrochemotherapy: a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues. *Biomed Pharmacother*. 2006;60:458–462. doi:10.1016/j.biopha.2006.07.016
56. Testori A, Tosti G, Martinoli C, et al. Electrochemotherapy for cutaneous and subcutaneous tumor lesions: a novel therapeutic approach. *Dermatol Ther*. 2010;23(6):651–661. doi:10.1111/j.1529-8019.2010.01370.x
57. Starita N, Di Monta G, Cerasuolo A, et al. Effect of electrochemotherapy on human herpesvirus 8 kinetics in classic Kaposi sarcoma. *Infect Agent Cancer*. 2017;12:35. doi:10.1186/s13027-017-0147-4
58. Di Monta G, Caracò C, Benedetto L, et al. Electrochemotherapy as "new standard of care" treatment for cutaneous Kaposi's sarcoma. *Eur J Surg Oncol*. 2014;40(1):61–66. doi:10.1016/j.ejso.2013.09.002
59. Campana LG, Testori A, Curatolo P, et al. Treatment efficacy with electrochemotherapy: a multi-institutional prospective observational study on 376 patients with superficial tumors. *Eur J Surg Oncol*. 2016;42(12):1914–1923. doi:10.1016/j.ejso.2016.06.399
60. Rotunno R, Campana LG, Quaglino P, et al. Electrochemotherapy of unresectable cutaneous tumours with reduced dosages of intravenous bleomycin: analysis of 57 patients from the International Network for Sharing Practices of Electrochemotherapy registry. *J Eur Acad Dermatol Venereol*. 2018;32(7):1147–1154. doi:10.1111/jdv.14708
61. Tourlaki A, Marzano AV, Brambilla L. Electrochemotherapy for Kaposi's sarcoma: all that glitters is not gold. *Eur J Dermatol*. 2023;34:89–90.
62. Tombolini V, Osti MF, Bonanni A, et al. Radiotherapy in classic Kaposi's sarcoma (CKS): experience of the Institute of Radiology of University "La Sapienza" of Rome. *Anticancer Res*. 1999;19(5C):4539–4544.
63. Chang JH, Kim IH. Role of radiotherapy in local control of non-AIDS associated Kaposi's sarcoma patients in Korea: a single institution experience. *Radiat Oncol J*. 2012;30(4):153–157. PMID: 23346533; PMCID: PMC3546282. doi:10.3857/roj.2012.30.4.153
64. Caccialanza M, Marca S, Piccinno R, Eulisse G. Radiotherapy of classic and human immunodeficiency virus-related Kaposi's sarcoma: results in 1482 lesions. *J Eur Acad Dermatol Venereol*. 2008;22(3):297–302. doi:10.1111/j.1468-3083.2007.02405.x
65. Hauerstock D, Gerstein W, Vuong T. Results of radiation therapy for treatment of classic Kaposi sarcoma. *J Cutan Med Surg*. 2009;13(1):18–21. PMID: 19298767. doi:10.2310/7750.2008.07076
66. Hernández Aragüés I, Pulido Pérez A, Suárez Fernández R. Inflammatory skin conditions associated with radiotherapy. *Actas Dermosifiliogr*. 2017;108(3):209–220. doi:10.1016/j.ad.2016.09.011
67. Spałek M. Chronic radiation-induced dermatitis: challenges and solutions. *Clin Cosmet Invest Dermatol*. 2016;9:473–482.
68. Tsao MN, Sinclair E, Assaad D, et al. Radiation therapy for the treatment of skin Kaposi sarcoma. *Ann Palliat Med*. 2016;5(4):298–302. doi:10.21037/apm.2016.08.03
69. Kirova YM, Belembaogo E, Frikha H, et al. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. *Radiother Oncol*. 1998;46(1):19–22. doi:10.1016/s0167-8140(97)00147-3

70. Singh NB, Lakier RH, Donde B. Hypofractionated radiation therapy in the treatment of epidemic Kaposi sarcoma--a prospective randomized trial. *Radiother Oncol*. 2008;88(2):211–216. doi:10.1016/j.radonc.2008.03.009
71. NCCN guidelines version 1.2024–Kaposi sarcoma. Available from: https://www.nccn.org/professionals/physician_gls/pdf/kaposi.pdf. Accessed November 9, 2023.
72. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. *Cancer*. 2010;116:3969–3977. doi:10.1002/cncr.25362
73. Gbabe OF, Okwundu CI, Dedicoat M, Freeman EE. Treatment of severe or progressive Kaposi's sarcoma in HIV-infected adults. *Cochrane Database Syst Rev*. 2014;8:CD003256.
74. Grolleau C, Walter-Petrich A, Dupin N, et al. Effectiveness and safety of major systemic treatments in classic and endemic Kaposi sarcoma: a multicentre retrospective study of 110 patients. *Br J Dermatol*. 2024;190(5):771–773. doi:10.1093/bjd/ljae032
75. Freeman EE, McCann NC, Semeere A, et al. Evaluation of four chemotherapy regimens for treatment of advanced AIDS-associated Kaposi sarcoma in Kenya: a cost-effectiveness analysis. *Lancet Glob Health*. 2022;10(8):e1179–e1188. doi:10.1016/S2214-109X(22)00242-X
76. Badalamenti G, Incorvaia L, Algeri L, et al. Safety and effectiveness of gemcitabine for the treatment of classic Kaposi's sarcoma without visceral involvement. *Ther Adv Med Oncol*. 2022;14:17588359221086829. doi:10.1177/17588359221086829
77. Zustovich F, Ferro A, Toso S. Gemcitabine for the treatment of classic Kaposi's sarcoma: a case series. *Anticancer Res*. 2013;33(12):5531–5534. PMID: 24324093.
78. Ramaswami R, Polizzotto MN, Lurain K, et al. Safety, activity, and long-term outcomes of pomalidomide in the treatment of Kaposi sarcoma among individuals with or without HIV infection. *Clin Cancer Res*. 2022;28(5):840–850.
79. Ramaswami R, Uldrick TS, Polizzotto MN, et al. A pilot study of liposomal doxorubicin combined with bevacizumab followed by bevacizumab monotherapy in patients with advanced Kaposi sarcoma. *Clin Cancer Res*. 2019;25(14):4238–4247. doi:10.1158/1078-0432.CCR-18-3528
80. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med*. 2016;374(26):2542–2552. doi:10.1056/NEJMoa1603702
81. Delyon J, Biard L, Renaud M, et al. PD-1 blockade with pembrolizumab in classic or endemic Kaposi's sarcoma: a multicentre, single-arm, Phase 2 study. *Lancet Oncol*. 2022;23:491–500. doi:10.1016/S1470-2045(22)00097-3
82. Zer A, Icht O, Yosef L, et al. Phase II single-arm study of nivolumab and ipilimumab (Nivo/Ipi) in previously treated classical Kaposi sarcoma (cKS). *Ann Oncol*. 2022;33(7):720–727. doi:10.1016/j.annonc.2022.03.012