

# Ultrasound as a tool to evaluate remission of cutaneous Kaposi's sarcoma

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**Objective:** To evaluate ultrasound measurement of Kaposi's sarcoma (KS) tumour volume for follow-up during therapy. Two-dimensional evaluation of size and description of gross alteration (for example, colour, nodularity, resolution) was used to assess treatment of KS. Flattening of palpable cutaneous KS lesions during anti-KS therapy has not been quantified objectively by a reliable method.

**Methods:** In six patients with advanced AIDS and KS, a total of 17 cutaneous lesions were evaluated prospectively by ultrasound and surface measurements. KS lesions were examined histologically before and after 12 weeks of chemotherapy with liposomal doxorubicin.

**Results:** In comparison with size reduction, volume measurement showed a more pronounced reduction of tumour volume. The mean tumour volume was reduced by 94% from  $451 \text{ mm}^3 \pm 655 \text{ mm}^3$  to  $66 \text{ mm}^3 \pm 165 \text{ mm}^3$  at week 12 ( $P < 0.001$ ). Histological evaluation of lesions no longer detectable by ultrasound after therapy showed abundant siderophages but no increase in spindle cells and no mitoses.

**Conclusions:** Our findings suggest that ultrasound is a useful method with which to follow growth and remission of cutaneous KS. In contrast, pigmentation due to iron deposition is unaffected by chemotherapy because, despite histological remission, pigmentation can persist. Though ultrasound cannot replace histologic evaluation for complete response, we suggest the use of ultrasound assessment, thus introducing a more objective criterion than subjective rating of nodularity.

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**Keywords:** AIDS, Kaposi's sarcoma, ultrasound, liposomal doxorubicin.

## Introduction

Cutaneous Kaposi's sarcoma (KS) is a nodular tumour of dark appearance. Pigmentation is caused by a high density of capillaries and by intracutaneous iron deposition [1]. To assess the efficacy of treatment for KS, two-dimensional evaluation of size ( $\text{mm}^2$ ) is used as well as description of gross alteration (for example, colour, nodularity, resolution). The heterogeneity of recruited subjects and lack of consistent response criteria make it difficult to compare studies of therapy for KS. The definition recommended by the AIDS Clinical Trial Group (ACTG) for a complete response requires histological documentation of the absence of malig-

nant cells in remaining pigmented areas [2]. Complete remission with restitution of normally coloured skin is achieved by chemotherapy in only a small proportion of lesions, and haemosiderin deposits may remain visible even when KS has otherwise resolved histologically.

Flattening of palpable cutaneous KS lesions during anti-KS therapy has not been quantified objectively by a reliable method. In an attempt to improve staging, we evaluated the use of ultrasound for measurement of tumour volume. Cutaneous Kaposi lesions show a characteristic sonographic pattern of low echogenicity in contrast to the hyperechoic surrounding subcutis.

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Thus, three-dimensional measurement of Kaposi lesions results in high accuracy for determination of tumour volume in follow-up evaluations.

## Subjects and methods

In a Phase I/II open trial we assessed dosage, efficacy and safety of intravenously administered liposomal doxorubicin in patients with advanced KS [3]. We introduced the parameter 'tumour volume' as assessed by sonographic measurement. Between November 1991 and June 1992, 32 male homosexual AIDS patients with advanced biopsy-confirmed KS were enrolled into the study (mean age, 38 years). Of these, 30 were caucasian and two were of Hispanic origin. Twenty-eight patients had KS stage III or IV according to the staging classification proposed by Mitsuyasu *et al.* [4]. Four patients had KS stage IIB with marked edema. Intravenous liposomal doxorubicin (Doxil<sup>®</sup>, Liposomal Technology, Manlo Park, California, USA) at doses of 10, 20 and 40 mg/m<sup>2</sup> was administered to 10, 19 and three patients every 2 weeks, respectively.

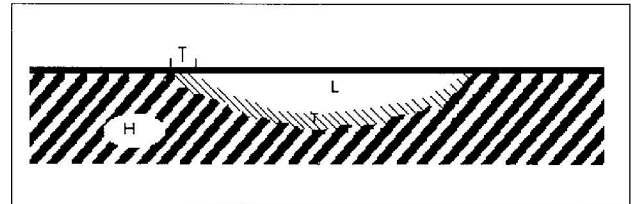
In each patient target lesions were defined and followed two-dimensionally during the trial. Six consecutive patients were selected for prospective additional ultrasound evaluation. A sample size of 17 lesions in six patients appeared sufficient for detection of differences between two- and three-dimensional measurement of KS lesions. Tumour status of those patients according to the ACTG criteria was T<sub>1</sub>I<sub>1</sub>S<sub>1</sub> in five cases and T<sub>0</sub>I<sub>0</sub>S<sub>1</sub> in one patient.

After verbal informed consent, six consecutively recruited patients were enrolled for ultrasound measurement in January 1992. The selection criteria for KS lesions were nodularity and accessibility. Lesions were clearly nodular and technically accessible by the ultrasound transducer were selected for each patient. Acral lesions, intertriginous lesions and lesions < 0.5 cm in diameter were excluded.

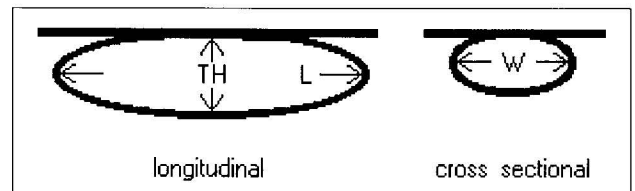
Each of the measurements at baseline and every 4 weeks thereafter included two-dimensional visible size of pigmented KS surface area, three-dimensional determination of tumour volume by ultrasound examination and colour-slide photographic documentation of identical lesions.

Ultrasound was performed using a 7.5 Megahertz linear transducer (Advanced Technology Laboratories Ltd, Seattle, Washington, USA; ULTRAMARK 5, Solingen, Germany). Sonomorphological characteristics of cutaneous KS lesions are low echogenicity, compared with the hyperechoic surrounding subcutaneous tissue, and relative homogeneity. Cutaneous KS lesions do not exhibit a clearly definable demarcation line. However, the border between subcutis and tumour is a zone of approximately 3 mm in which the tran-

sition from high to low echogenicity is seen. A central point in the transition area was chosen for measurement as a surrogate for a clear demarcation line (Fig. 1). Longitudinal and cross measurement was taken at the site of the greatest diameter of each lesion (Fig. 2). Volumes were computed according to the formula for approximation of ellipsoids [(length × width × thickness)/2].



**Fig. 1.** Diagram of characteristic sonographic appearance of cutaneous Kaposi's sarcoma (KS) as depicted by 7.5 MHz linear transducer. H, highly echogenic surrounding subcutis; T, transition zone from high to low echogenicity; L, low echogenicity of KS.



**Fig. 2.** Schematic diagram of measurement procedure using the approximation for ellipsoid structures. L, length; TH, thickness; W, width.

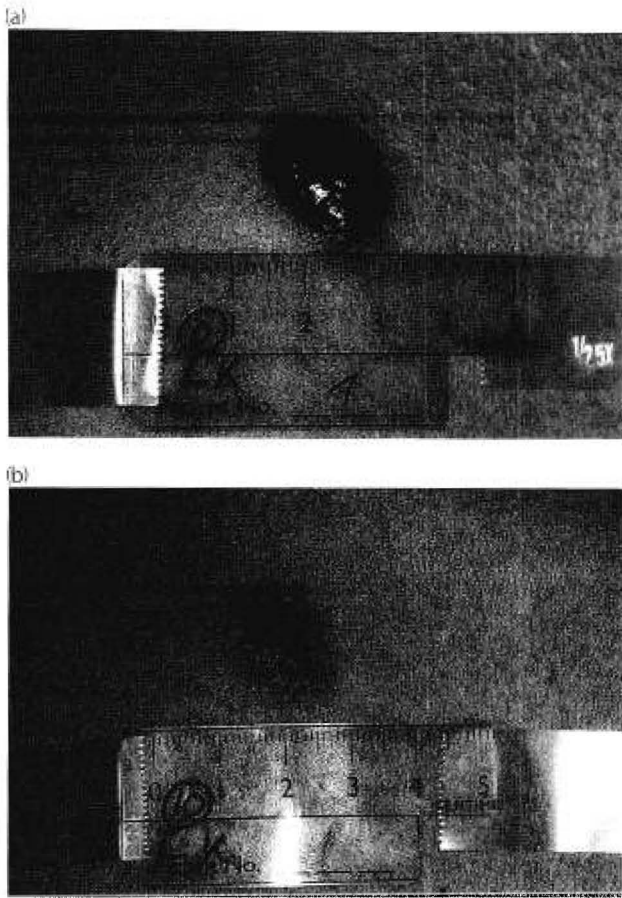
Ultrasound evaluations were performed by three different examiners (JRB, MH, and SS). Measurements obtained were comparable. To avoid systematic errors due to inter-individual differences, follow-up examinations were performed by the same examiner who documented the baseline volume.

In three out of the six patients, additional post-therapy punch biopsies were taken from those cutaneous KS that had been followed by ultrasound examination. For histological examination, sections of formalin embedded material were stained with haematoxylin and eosin, Elastica van Giesson and Berliner-Blau iron staining.

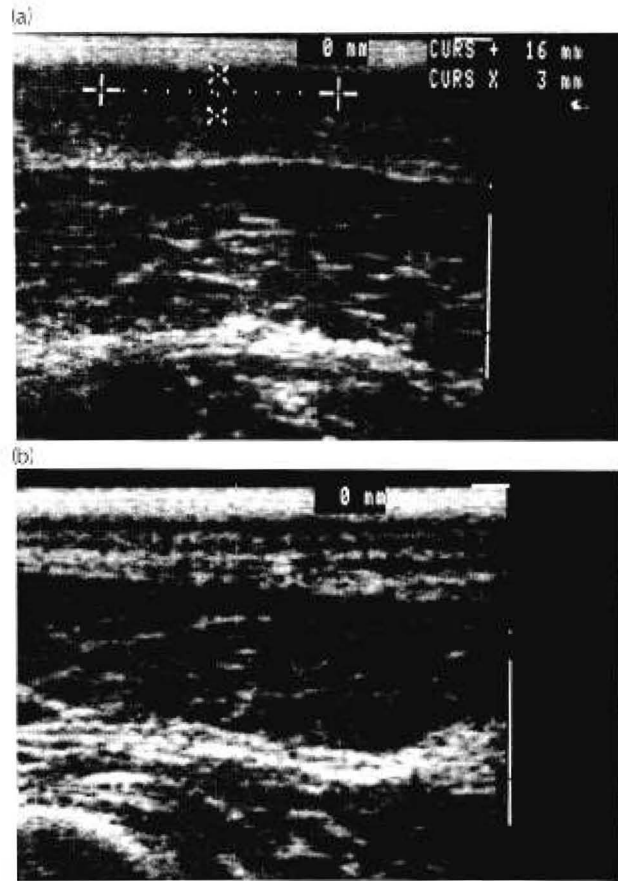
Statistical analysis was performed by analysis of variance and Student's t-test.

## Results

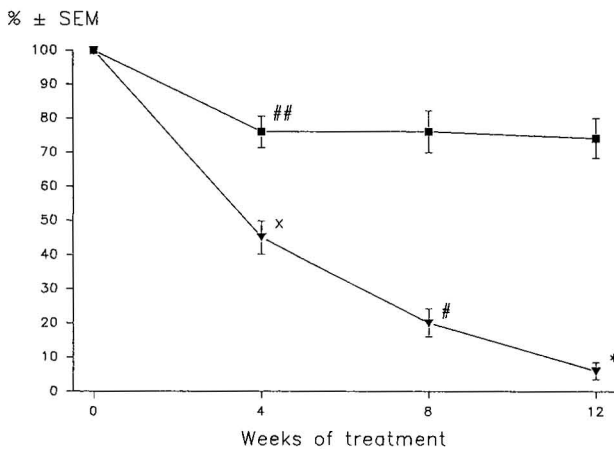
At week 12, after six cycles of liposomal doxorubicin, there was a visible reduction of KS size by 26% from 288 mm<sup>2</sup> ± 354 mm<sup>2</sup> at baseline to 210 mm<sup>2</sup> ± 296 mm<sup>2</sup> ( $P < 0.05$ , by t-test for paired samples). Visible response was documented by photographs showing a flattening of tumour lesions that appeared nodular prior to therapy (Fig. 3a versus Fig. 3b).



**Fig. 3.** Kaposi's sarcoma (KS) lesion before and at week 12 of chemotherapy with liposomal doxorubicin. (a) A clearly nodular KS lesion, which appears flattened after therapy (b).



**Fig. 5.** Sonographic examination of the Kaposi's sarcoma lesion depicted in Fig. 3. (a) Tumour length and thickness is indicated by + — + and x — x. (b) After therapy, the tumour is no longer detectable by ultrasound.



**Fig. 4.** Reduction of Kaposi's sarcoma (KS) size (■) and volume (▼) during chemotherapy with liposomal doxorubicin at baseline and weeks 4, 8 and 12. While two-dimensional measurement of size does not show further reduction after week 4, tumour volume, as determined by ultrasound, reveals a significant reduction at each interval. \* $P < 0.05$  versus baseline and versus week 4, <sup>†</sup> $P < 0.05$  versus baseline, <sup>‡</sup> $P < 0.005$  versus baseline, <sup>§</sup> $P < 0.001$  versus baseline and  $P < 0.01$  versus week 8.

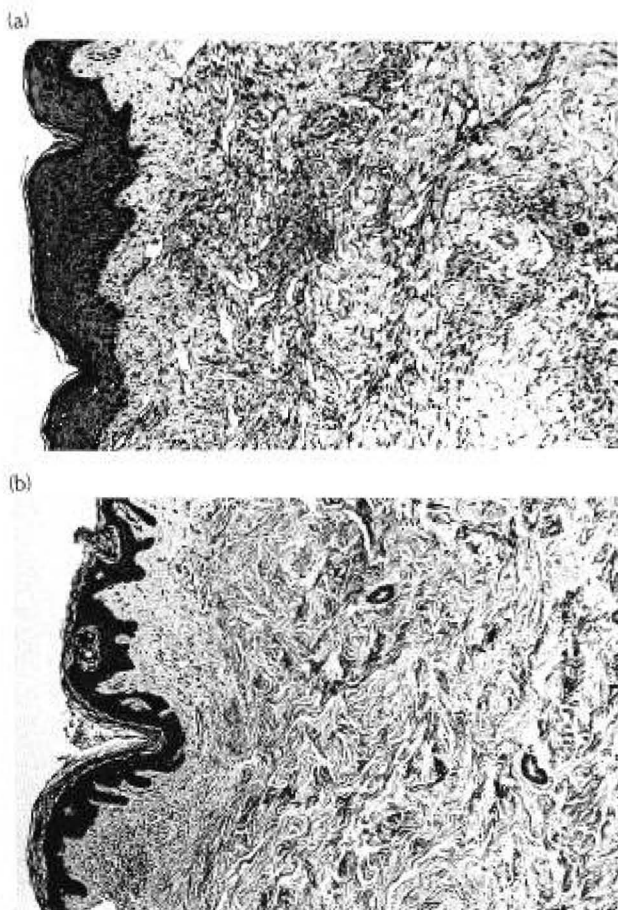
Determination of tumour volume by ultrasound revealed a reduction by 94% from  $451 \text{ mm}^3 \pm 655 \text{ mm}^3$  to  $66 \text{ mm}^3 \pm 165 \text{ mm}^3$  ( $P < 0.001$ ) at week 12. The mean volume at week 4 ( $225 \text{ mm}^3 \pm 401 \text{ mm}^3$ ) and

week 8 ( $115 \text{ mm}^3 \pm 196 \text{ mm}^3$ ) was significantly reduced, compared with baseline ( $P < 0.05$ ). Reduction of volume from weeks 4 to 8, and from weeks 8 to 12 was significant, as shown in Fig. 4 ( $P < 0.01$ ). Figure 5 shows two representative ultrasound images of the lesion depicted in Fig. 3, prior to and after therapy.

Histological examinations at baseline showed an increased number of irregular-shaped and sometimes dilated vessels in all levels of the dermis, which were lined by thin endothelial cells as well as spindle-shaped cells in short fascicles. Perivascular plasma cells were noted and siderophages were found in abundance (Fig. 6a).

After therapy, biopsies were obtained in three patients targeting the identical site that had been followed-up clinically (Fig. 3b) and by ultrasound (Fig. 5b).

The biopsies taken after 12 weeks of treatment with liposomal doxorubicin showed a slightly increased number of inconspicuous and sometimes irregular-shaped thin-walled vessels, lined by flat cells without mitoses or marked cytologic atypia in the upper half of the reticular dermis around the superficial and periadnexal vascular plexus. No increase in the number of spindle cells and clefts between collagen bundles was seen, but abundant siderophages and a slight fibrosis



**Fig. 6.** (a) Histology of a Kaposi's sarcoma (KS) excided from the same patient shown in Figs 3 and 5 prior to therapy; plaque stage of KS (haematoxylin and eosin  $\times 250$ ). (b) Histologic picture of the lesion depicted in Figs 3b and 5b after therapy. In the lower half of the reticular dermis there are some siderophages and a slight fibrosis, but no spindle cells (haematoxylin and eosin  $\times 150$ ).

were found in the lower half of the reticular dermis (Fig. 6b).

## Discussion

Measurement of KS surface in two (visible) dimensions suggests minor reduction in size while sonographic evaluation might indicate extensive remission. Since a haemosiderin deposits in the skin may remain visible for extended periods of time, despite successful treatment of tumour cells, sonographic assessment appears more appropriate. The response criteria for KS evaluation developed by the Oncology Committee of ACTG recommend that the character of KS lesions is noted and evaluated [2]. Instead of using a grading of 'nodularity', which relies on the personal judgement of the investigator, we sought to identify a more objective method of measurement. Ultrasound has been proposed as a harmless diagnostic aid to clinical examination of proliferative vascular lesions of the skin [5], such as lymphangiomas and haemangiomas. Betti *et al.* [5] reported a 'mixed sono-

graphic structure with ill-defined margins' using high resolution ultrasonography with 20 MHz transducers. However, our experience of using a linear 7.5 MHz transducer showed that discrimination of KS tumours and surrounding subcutis is adequate although there is no clear demarcation of the tumour. Thus, determination of tumour volume in the natural course of KS or tumour regression during chemotherapy can be performed with sufficient reliability. However, further prospective analysis of inter-individual reproducibility of ultrasound examinations is necessary and ongoing at present.

Our findings suggest that ultrasound is a useful method for follow-up of growth and remission of cutaneous KS. Moreover, ultrasound evaluation is more closely related to the effect of chemotherapy in the remission of KS, showing a reduction in tumour volume that can be histologically proven by lack of tumour cells. In contrast, pigmentation due to iron deposition is not affected by chemotherapy and is an unreliable parameter of its efficacy.

Ultrasound examination can only be applied to a limited number of lesions, and tumour response cannot be based solely on one to three lesions. However, histologic examination can be performed on only one lesion and still confirm a response. The assessment of total tumour burden, and the appearance of new lesions and the visceral disease must also be evaluated.

In general, siderophages are not abundant in macules or patches of KS [1]. The lesions seen before treatment showed clinical features of nodularity and histological features characteristic of the plaque stage of KS, combining the structure of patch and nodular lesions [6]. On lesions that were clearly nodular prior to therapy (clinically and as determined by ultrasound), punch biopsy was performed after treatment. The histologic features of early patch stages of KS were detectable. Nevertheless, these lesions showed an increased number of siderophages in the dermis as well as slight fibrosis. Thus, the response detected by ultrasound (shrinking of volume to zero) was confirmed histologically after therapy.

According to the ACTG's recommendation [2] histological absence of malignant cells is required for a complete response diagnosis. However, biopsy prior to and after a trial is not readily obtainable and includes an invasive procedure. Ultrasound measurement and documentation of volume reduction is thus an easily applicable alternative. In patients in whom skin biopsy cannot be obtained (no consent, contra-indications), ultrasound may provide an alternative measurement. However, histological evaluation for confirmation of complete response cannot be replaced by ultrasound.

We suggest that clinical trials use ultrasound assessment of remission of cutaneous KS to evaluate new treatment regimens.

## References

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