Doppler US with perfusion software and contrast medium injection in the early evaluation of isolated limb perfusion of limb sarcomas: prospective study of 49 cases

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Background: The aim of this study was to prospectively evaluate the use of Doppler ultrasonography with perfusion software and contrast agent injection (DUPC) during isolated limb perfusion (ILP) with high-dose chemotherapy and TNF-α (biochemotherapy) in patients with locally advanced extremity soft tissue sarcoma (STS).

Patients and methods: Fifty-two patients were prospectively included in this monocentric imaging trial. Three were excluded because the study was incomplete in two patients and one tumour did not exhibit any contrast uptake. DUPC was performed before ILP and on days 1, 7, 15, 30 and 60 after ILP. A total of 292 DUPC were performed on 55 target lesions in 49 evaluable patients. The percentage of contrast uptake was evaluated at each tumour site by two radiologists. The criterion tested was a decrease of more than 50% in intra-tumour contrast uptake compared to the pre-ILP examination. Results were compared with both MRI and histological analysis after resection of residual disease.

Results: According to MRI and the histological analysis, 25 (51%) patients were good responders (no difference between the four treatment arms) with tumour necrosis exceeding 90% and 24 (49%) were poor responders. As of day +1, the accuracy of DUPC in predicting tumour response was 82% (18/25 good responders and 22/24 poor responders) increasing to 91% at day +7, 95% at day +15 and 96% at day +30. At day +15, DUPC was predictive of a good response in 100% of the cases.

Conclusion: DUPC is a simple technique, allowing early prediction of tumour response after ILP. A new treatment planning scheme can be proposed based on the results of this study.

Key words: biochemotherapy, contrast medium, isolated limb perfusion, magnetic resonance imaging (MRI), soft tissue sarcoma (STS), ultrasound (US)

Introduction

Isolated limb perfusion (ILP) is a local treatment allowing high doses of anticancer agents to be delivered to a limb that has been surgically isolated from the systemic circulation. In locally advanced soft tissue sarcoma (STS), the aim of this procedure is to achieve tumour volume shrinkage and/or to induce complete tumour necrosis so that conservative oncological surgery can be performed, avoiding amputation. Resection of residual disease is usually performed 2 months after ILP.

ILP was first used in recurrent melanomas, and then in STS of the extremity [1]. In 1992, Lienard et al. [2] used TNF-α and demonstrated a very high response rate with limb-salvage rates attaining 80%. In 1999, Eggermont et al. [3] reported the results of a multicentric European study on 246 patients with limb sarcoma. The objective response rate was 75% including 28% of complete responses. This procedure is safe and has been reported to yield excellent results, even in elderly patients over 75 years of age [4]. MR imaging (MRI) is the technique currently used to evaluate the effectiveness of ILP in STS [5]. The aim of this study was to use Doppler ultrasonography with perfusion software and contrast agent injection (DUPC) to predict tumour response to chemotherapy and TNF-α as early as possible, in locally advanced STS of the extremity in patients undergoing ILP and to compare this technique with MRI.

Patients and methods

Patients

The study was approved by our Institutional Review Board. Fifty-two patients with locally advanced STS were prospectively included in this
monocentric imaging trial. Patients included came from a large multi-centre randomised study testing four different doses of TNF-α (0.5, 1, 2, and 3 or 4 mg). The definitive results of this recently reported trial demonstrated no statistical difference between the four treatment arms in terms of objective regression and histological response [6]. The results will be published elsewhere. One tumour did not exhibit any contrast uptake and was excluded from this study. The study was not completed in two patients.

Materials

Two sonographs, a Powervision 8000 and an Aplio (Toshiba, Japan) were used with a 4.4 MHz convex-array or a 12 MHz linear transducer equipped with a dynamic flow perfusion software, which produces rapid imaging of flow with excellent spatial resolution and suppression of the blooming effect. Dynamic flow employs wide-band transmission pulses as short as those used in B-mode imaging, thereby significantly improving distance resolution. The Doppler digital image optimizer (DIO) is a processing technique that uses a wall filter to distinguish tissues from blood flow. It employs a special algorithm to determine whether a signal originates from blood flow or from tissues. Adaptative image processing (AIP) is an algorithm used to generate a composite image comprising a B-mode image and a Colour angio-image acquired through wide-band transmission and with the DIO.

DUPC were performed the day before ILP and on days 1, 7, 15, 30 and 60 after ILP. Each DUPC was performed in four steps.

1. The morphological study was performed in B mode. This allowed us to identify the target lesion and to select the best acoustic window for its assessment. The largest diameters of each lesion were measured with calipers. We recorded echogenicity and heterogeneity or homogeneity in appearance.

2. Doppler study before i.v. injection. Colour Doppler US was used for all examinations with sensitivity adjustment adapted to slow flow (pulse repetition frequency: 0.5–4.5 kHz) and dynamic flow. Vessels visualised inside the tumour were counted.

3. Injection of sonographic contrast agent. Levovist* (SHU 508 A, Schering*, Berlin, Germany) is a suspension of μm-sized microparticles of galactose and microscopic gaseous bubbles combined with a very weak concentration of palmitic acid prepared by gently shaking 4 g of microparticles in sterilised water for 10 s and leaving them to settle for 2 min. This

<table>
<thead>
<tr>
<th>Tumour histological types</th>
<th>Good response</th>
<th>Poor response</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial sarcoma</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumour</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Epithelial sarcoma</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myxoid sarcoma</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Alveolar sarcoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>24</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 1. Tumour response according to tumour histological type

Table 2. Evolution of the mean percentage of tumour contrast uptake between day –1 before ILP and the successive DUPC after ILP according to tumour response evaluated with MRI and the histological analysis

<table>
<thead>
<tr>
<th>Day</th>
<th>Good tumour response</th>
<th>P</th>
<th>Poor tumour response</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day –1</td>
<td>58.7%</td>
<td>&lt;10⁻⁴</td>
<td>53.1%</td>
<td>0.5</td>
</tr>
<tr>
<td>Day +1</td>
<td>19.4%</td>
<td>0.07</td>
<td>52.4%</td>
<td>0.5</td>
</tr>
<tr>
<td>Day +7</td>
<td>19.4%</td>
<td>&lt;10⁻⁴</td>
<td>45.2%</td>
<td>0.1</td>
</tr>
<tr>
<td>Day +15</td>
<td>18.6%</td>
<td>&lt;10⁻⁴</td>
<td>51.9%</td>
<td>0.8</td>
</tr>
<tr>
<td>Day +30</td>
<td>13.5%</td>
<td>&lt;10⁻⁴</td>
<td>46.3%</td>
<td>0.07</td>
</tr>
<tr>
<td>Day +60</td>
<td>11.1%</td>
<td>&lt;10⁻⁴</td>
<td>43.6%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

1. The morphological study was performed in B mode. This allowed us to identify the target lesion and to select the best acoustic window for its assessment. The largest diameters of each lesion were measured with calipers. We recorded echogenicity and heterogeneity or homogeneity in appearance.

2. Doppler study before i.v. injection. Colour Doppler US was used for all examinations with sensitivity adjustment adapted to slow flow (pulse repetition frequency: 0.5–4.5 kHz) and dynamic flow. Vessels visualised inside the tumour were counted.

3. Injection of sonographic contrast agent. Levovist* (SHU 508 A, Schering*, Berlin, Germany) is a suspension of μm-sized microparticles of galactose and microscopic gaseous bubbles combined with a very weak concentration of palmitic acid prepared by gently shaking 4 g of microparticles in sterilised water for 10 s and leaving them to settle for 2 min. This

Figure 1. Neurosarcoma of the knee in a 54-year-old woman. Doppler imaging the day before ILP. (A) The hypoechoic tumour measured 62.6 × 36.6 mm. (B) Colour Doppler study depicted neovascularisation in the tumour. (C) DUPC shows intra-tumour vascularisation a few seconds after injection of Levovist*. (D) 18 s after the last image, contrast uptake is about 80%. (E) DUPC at day +1 after ILP confirmed that neovascularisation was totally eradicated; contrast agent is visible only in the normal tissue surrounding the tumour but not in the tumour. (F) DUPC at day +60 demonstrates total tumour necrosis with no contrast uptake in the very hypoechoic necrotic tumour. MRI at day +60. (G) Sagittal T1-W fat-sat image after contrast medium = necrotic lesion, with uptake only in the wall. (H) Superimposition of the axial dynamic image (colour) and the T1-W fat-sat image. Minimal uptake in the thin wall of the lesion. Complete tumour necrosis was confirmed by histology.
yields a suspension of 10 ml at a concentration of 400 mg/ml that must be injected intravenously, at a rate of 1 ml/s. Ninety-five per cent of the micro-bubbles measure less than 10 μm in diameter, and 50% are less than 3 μm in diameter.

4. Dynamic study after injection of Levovist®. Signal enhancement of intratumour neovessels was evaluated visually in real time and the dynamic sequence was recorded on a digital tape. We recorded the time when the contrast agent was injected, the time when enhancement began...
and when maximal enhancement was attained. Every subjective or objective reaction was also recorded.

With dynamic flow, the emission power must be set to obtain a mechanical index (MI) high enough to explode the Levovist® microbubbles and to enhance the signal of all vascularised tissues. Transducer sweeping was stopped for 3–5 s almost every 10 s to allow the microbubbles to accumulate further in tiny foci of residual tumour tissue. The explosion of accumulated microbubbles was revealed by signal enhancement at resumption of transducer sweeping.

The examinations recorded were reviewed by two radiologists who visually evaluated the percentage of the tumour volume taking up contrast agent at the time of maximal enhancement. The percentage of intra-tumour contrast uptake depended on parenchymal vascularisation, which signified the presence of viable residual tumour tissue.

MR imaging was performed at 1.5 T (GE Medical Systems, Milwaukee, WI). The examinations always included T1-weighted SE and fast SE T2-weighted fat-saturated sequences, as well as dynamic sequences (T1-weighted SE repeated six times every 40 s, TR 300 ms, 128 acquisitions displaying the maximum intensity slope in each pixel), and SE T1-weighted frequency-selective fat suppression after the dynamic sequence. Necrosis was defined as no uptake inside the tumour on sequences after injection of contrast agent. On dynamic sequences, behaviour identical to that of an artery was considered indicative of active tumour, and late contrast uptake signalled inflammatory changes without tumour.

Response criteria

With MRI, a good response to ILP was defined as tumour necrosis exceeding 90% at day +30 and/or at day +60 with histological correlation. On DUPC, a decrease in contrast uptake exceeding 50% compared with the pre-ILP examination, with or without a decrease in tumour size, was considered an objective response. We chose 90% instead of 90% required by MRI and histology because our aim was to determine an earlier response criterion and because a decrease of 50% was easy to evaluate as early as day +1 after ILP.

Table 3. Comparison between the mean percentage of tumour contrast uptake on DUPC and the percentage of tumour necrosis on MRI and tumour necrosis at histological analysis between good and poor responders

<table>
<thead>
<tr>
<th></th>
<th>DUPC day +15</th>
<th>DUPC day +30</th>
<th>DUPC day +60</th>
<th>MRI day +30</th>
<th>MRI day +60</th>
<th>Histological tumour necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good tumour response</td>
<td>18.6%</td>
<td>13.5%</td>
<td>11.1%</td>
<td>84%</td>
<td>90.5%</td>
<td>90%</td>
</tr>
<tr>
<td>Poor tumour response</td>
<td>51.9%</td>
<td>46.3%</td>
<td>43.6%</td>
<td>34.8%</td>
<td>30.6%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table 4. Predictive value of DUPC for tumour response to ILP in relation to MRI and the histological analysis. The criterion tested was a decrease in contrast uptake exceeding 50% on two successive DUPC

<table>
<thead>
<tr>
<th>DUPC</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>No. of tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day +1</td>
<td>21</td>
<td>3</td>
<td>24</td>
<td>7</td>
<td>75%</td>
<td>89%</td>
<td>87%</td>
<td>77%</td>
<td>82%</td>
<td>55</td>
</tr>
<tr>
<td>Day +7</td>
<td>24</td>
<td>1</td>
<td>26</td>
<td>4</td>
<td>86%</td>
<td>96%</td>
<td>96%</td>
<td>87%</td>
<td>91%</td>
<td>55</td>
</tr>
<tr>
<td>Day +15</td>
<td>25</td>
<td>0</td>
<td>27</td>
<td>3</td>
<td>89%</td>
<td>100</td>
<td>100</td>
<td>90%</td>
<td>95%</td>
<td>55</td>
</tr>
<tr>
<td>Day +30</td>
<td>27</td>
<td>1</td>
<td>26</td>
<td>1</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
<td>55</td>
</tr>
<tr>
<td>Day +60</td>
<td>29</td>
<td>1</td>
<td>22*</td>
<td>1</td>
<td>97%</td>
<td>96%</td>
<td>97%</td>
<td>96%</td>
<td>96%</td>
<td>53*</td>
</tr>
</tbody>
</table>

*Two patients were amputated between day +30 and day +60.

TP, true positive; FP, false positive; TN, true negative; FN, false negative; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Statistical analysis

Results obtained by DUPC were compared with MRI results. DUPC and MRI results were compared with surgery and the pathological response. Statistical analyses were performed with the Period T-test.

Results

The results presented concern 49 patients, 27 males and 22 females, aged from 8 to 81 years (median ± SD, 50.6 ± 15.2 years), with a total of 55 lesions. Tumour sites were the upper limbs and the lower limbs in 24 and 25 cases, respectively. Tumour types were synovial sarcoma (n = 12), liposarcoma (n = 10), malignant peripheral nerve sheath tumour (n = 5), fibrosarcoma (n = 4), epithelial sarcoma (n = 4), leiomyosarcoma (n = 4), undifferentiated sarcoma (n = 3), malignant fibrous histiocytoma (n = 2), myxoid sarcoma (n = 2), rhabdomyosarcoma (n = 1), angiosarcoma (n = 1) and alveolar sarcoma (n = 1) (Table 1). A total of 292 DUPC were performed: 49 before ILP, 49 at day +1, day +7, day +15, day +30 and 47 at day +60 (two patients were amputated between day +30 and day +60). Forty-nine and 47 MRI were performed at day 30 and day 60, respectively.

Twenty-five patients with a total of 31 lesions were good responders and 24 patients with 24 lesions were poor responders according to MRI and histological criteria. There was no correlation between the tumour size before ILP and tumour response and between tumour response at 2 months and the tumour histological type. No correlation was found between tumour response and the percentage of contrast uptake at DUPC before ILP. In the group of good responders, 13/31 (42%) tumours exhibited contrast uptake exceeding 80% before ILP; only 9/24 (38%) did in the group of poor responders. Sixteen tumours were poorly vascularised on DUPC.
before ILP (<20% of contrast uptake). Nine of these tumours exhibited a good response and seven a poor response. On DUPC at day +1 there were four false-negatives (FN) and two false-positives (FP) according to the response predicted in this group. A strong correlation was found between a decrease in uptake exceeding 50% at day +1 after ILP and tumour response (Table 2).

**Good tumour response**

Among the good responders, a decrease in contrast uptake exceeding 50% at day +1 after ILP was observed in 21/31 tumours (Figure 1). This 50% decrease occurred at day +7 in three more tumours, at day +15 in one tumour and at day +30 in two tumours. In two patients, the good response was delayed and observed only at day +60 on DUPC and MRI.

In one case a decrease in contrast uptake exceeding 50% was seen at day +1 and day +7 but not confirmed at day +15 and day +30. A good response occurred at day +60 with necrosis exceeding 90% on MRI and 0% vascularity on DUPC.

There was one false-negative DUPC study with no significant decrease in contrast uptake and complete necrosis on MRI. In this tumour, vascularity was very poor (5%–10%) on DUPC and the changes from one examination to the following study were not significant.

In the group of good responders, there were no changes in the extent of tumour necrosis on MRI between day +30 and day +60 in 26/31 tumours (Table 3). In four cases, tumour necrosis increased significantly between day +30 and day +60. In one patient, the tumour size did not change by day +30, but it became completely necrotic with a thin wall. After this initially good result, MRI depicted less than 50% of necrosis and a larger vascularised tumour volume by day +60 with thickening of the tumour wall.

**Poor tumour response**

In 11 tumours, the percentage of contrast uptake was unmodified the day after treatment, it had increased in four and the decrease was less than 30% in seven (Figure 2). In two cases, a decrease of 50% in contrast uptake was observed at day +1 but not confirmed at day +7.

On MRI, tumour necrosis was less than 70% at day +30 in 23/24 patients (mean 30%). Two of these patients had to be amputated because of tumour progression. On MRI at day +60, tumour necrosis was less than 70% in 21/22 tumours (mean 30%). There was one false-positive MRI due to misinterpretation: the signal of a differentiated liposarcoma was mistaken for the signal indicating necrosis. The vascularity of this tumour was poor, evaluated at 10% on DUPC, with no changes on successive examinations.

The predictive value of DUPC for tumour response is shown in Table 4. As early as day +1, the positive predictive value (PPV) was 87%. The three false-positives (a decrease exceeding 50% in contrast uptake, which was not confirmed on further examinations) were probably due to an early oedematous reaction after ILP without true destruction of tumour vessels. At day +1 there were seven false-negatives, six being due to no decrease in tumour vascularity at day +1. However, the response was delayed and the vascularity decreased later. In a poorly vascularised tumour there was no significant decrease in contrast uptake on DUPC, but necrosis was complete on MRI.

At day +15, a decrease exceeding 50% in tumour vascularity was predictive of a good response in 100% of the cases (25 tumours). There was no positive response on DUPC in 30 tumours, 24 of which were true poor responses. In five cases, the response occurred later and one was a false-negative on DUPC.

At day +30, MRI and DUPC were concordant in 20/25 good responders and 22/24 poor responders (Figure 3). Compared with histological data, there was one false-positive but no false-negatives on MRI at day +60.

In all of our cases, DUPC was technically possible without complications or adverse reactions after intravenous contrast agent injection.

**Discussion**

ILP is an aggressive local treatment modality that allows high doses of anticancer agents to be delivered to a limb that has been surgically isolated from the systemic circulation.

A high complete remission rate was first obtained in patients with melanoma using the drug melphalan while continuously monitoring systemic leakage [7]. ILP subsequently yielded good results in patients with STS when tumour necrosis factor (TNF-α) was added to melphalan. TNF-α induces necrosis of tumour vessels and allows greater intra-tumour penetration of chemotherapy when combined with hyperthermia. The addition of high-dose TNF-α to the perfusate results in a four- to six-fold increase in melphalan and doxorubicin accumulation in the tumour [8]. A response rate of 89% has been reported in melanomas and locally advanced STS [2]. In STS, the aim of ILP is to achieve tumour volume shrinkage and to induce tumour necrosis so that amputation can be avoided and the patient’s quality of life can be improved. The success rate is about 80% in different series [9–11]. In our experience, conservative limb-sparing surgery was possible in about 80% of the patients and about 50% had a good response on MRI with tumour necrosis exceeding 90% [6].

MRI is the gold-standard technique for evaluating STS of the extremity before and after loco-regional and/or systemic treatments [12]. World Health Organisation criteria [13] or RECIST (Response Evaluation Criteria in Solid Tumour) criteria [14] are not adapted because total tumour necrosis is often obtained without a decrease in the tumour volume. A functional imaging technique seems to be required to evaluate the percentage of tumour necrosis which may be a more accurate predictor of chemosensitivity than the clinical and/or radiological response [15, 16]. PET was used to evaluate the response 2 weeks after ILP, but specificity was poor. It seems to be useful before ILP for the selection of candidates in whom such treatment is likely to be efficient [17].
On MRI, a complete response is defined as either the disappearance of the tumour or a totally necrotic lesion, with or without a decrease in volume. In our study, tumour necrosis exceeding 90% on MRI was considered a good response that was correlated with the post-surgical histological analysis. Histologically, less than 10% of viable cells are considered a good response in STS. However, comparing the histological, clinical and imaging responses can be difficult because the histological analysis does not take into account the initial tumour size. The tumour volume may shrink drastically while 100% of viable cells are found in a very small residual lesion. In such cases, response is under-evaluated compared with clinical and imaging results.

High-frequency Doppler ultrasonography is able to detect neovascularisation in animal tumour models [18] and in human tumours [19, 20]. Since 1999, contrast-enhanced ultrasonography has been used to optimise the detection of angiogenesis. This technique has benefited from major technological improvements, such as digitisation and electronic processing of the ultrasound signal, as well as the multiplicity of transducer channels allowing enhanced resolution and greater sensitivity for micro-vessel detection [21].

Imaging of slow flow has also improved as a result of technical innovations [22]. The use of contrast agents allows enhancement of the signal emitted by vessels and even neovessels as tiny as 40 microns in diameter are detectable [23]. The study of tumour neovascularisation is currently of major import in imaging research as it can be used to evaluate the efficiency of new anti-angiogenic treatments and the metastatic potential of tumours [24, 25].

We could have expected higher activity with high-dose TNF-α in vascularised soft-tissue tumours than in poorly vascularised tumours, but such was not the case. Our results show that the degree of tumour vascularity evaluated with pretreatment DUPC is not predictive of tumour response. Changes in tumour vascularity were less accurately evaluated with DUPC in poorly vascularised tumours. Among the 16 tumours with less than 20% of contrast uptake before ILP, it was difficult to predict the response at day +1 in nine. The aim of DUPC the day before ILP is not to select patients for ILP but to evaluate the degree of tumour vascularity and to identify patients in whom evaluation with DUPC after ILP will be useful and accurate.

As early as day +1, the accuracy of DUPC in predicting responses was 82%. We found no pre-ILP predictive factors to explain why about 50% of the tumours exhibited a very early dramatic decrease in vascularity and 50% did not. Neither the tumour size, pre-ILP tumour vascularity, nor the histological type were significantly different between the two groups.

At day +15, the PPV of DUPC was 100%. It will therefore be possible to propose a new follow-up and treatment planning scheme after ILP with an initial DUPC evaluation at day +15 and, if the response is good, an MRI examination, not only to confirm tumour necrosis but also to obtain a pre-surgical topographic study. Currently, surgery is performed 2 months after ILP, which is the usual timing. Conservative limb-sparing surgery is technically possible 1 month after ILP.

If our new management scheme had been implemented in our series, 18 of the 49 patients (37%) would have been operated on earlier, even before 1 month after ILP. Moreover, the further increase in tumour volume between the first and second month after treatment in the patient in our series could have been avoided had we operated earlier. It should be borne in mind that this re-progression after complete necrosis is not exceptional as it also occurred in three cases in another series [12].

If there is no response or it is poor on DUPC at day +15, then a new evaluation could be obtained at day +30 with DUPC and MRI. If there is no response or it is poor at day +30, it is worth waiting 2 months in order to avoid an amputation that may turn out to be unnecessary. If tumour response is still poor at 2 months, the initial surgical treatment plan (amputation or wide resection) should be reconsidered.

Conclusion

DUPC is a simple, non-invasive imaging technique that allows early and accurate evaluation of tumour response in patients undergoing ILP with high-dose chemotherapy and TNF-α. The decrease in contrast uptake assessed by DUPC the day after ILP was correlated with a favourable histological response. DUPC results are comparable to those of MRI but are available earlier because Doppler US examinations are easy to perform, even when there are strong inflammatory reactions after treatment. The patient can be examined in bed and the results are immediately available. In all of our cases the examination was technically possible without complications. A new treatment planning scheme can now be proposed, based on the results of this study.

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