

# Intraperitoneal antineoplastic drug delivery: rationale and results

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The use of intraperitoneal drug delivery in the treatment of malignant disease confined to the peritoneal cavity is based on the theoretical potential for increased exposure of the tumour to antineoplastic agents leading to improved cytotoxicity. Phase I studies have explored the safety and pharmacokinetic advantage of the regional administration of several drugs, including cisplatin (10 times higher than systemic delivery) and paclitaxel (1000 times higher). Phase II trials of second-line intraperitoneal chemotherapy of ovarian cancer, generally with cisplatin, have shown the potential for patients to achieve surgically-documented complete responses. Randomised trials of second-line regional therapy in patients with ovarian cancer have yet to be conducted, although non-randomised single institution experience has suggested the potential for long-term disease-free survival with this strategy. By contrast, several well-planned randomised trials of first-line intraperitoneal chemotherapy of small-volume residual advanced ovarian cancer after primary surgical cytoreduction have reported a survival advantage with regional drug delivery. Although a rationale can be proposed for intraperitoneal antineoplastic drug delivery in non-ovarian malignant disease involving the peritoneal cavity, current data do not support the use of this strategy outside the confines of well-designed clinical trials.

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The direct intraperitoneal administration of antineoplastic agents has been studied in investigative trials and used in clinical practice for more than 40 years.<sup>1</sup> The fundamental goal of intraperitoneal administration is to increase the exposure of cancer cells within the peritoneal cavity to the drug while minimising potential toxic effects to internal organs (figure 1). Initial efforts to exploit the potential for increased regional and decreased systemic drug concentrations focused on controlling the formation of malignant ascites. Although clinical benefit is occasionally observed with this approach, it remains uncertain if a reduction in reaccumulation of cavity fluid results from a direct cytotoxic effect, or (more likely) is due to an indirect effect caused by the sclerosing potential of such drugs on the cells lining the peritoneal cavity. Concern about the local toxic effects of regional delivery and the recognition that large tumour masses essentially never regressed, even with a disappearance of ascites, markedly reduced the enthusiasm for this management strategy, except to provide symptomatic relief.<sup>2</sup>

## Rationale for intraperitoneal drug delivery

In the late 1970s, interest in intraperitoneal drug delivery was renewed after the publication of a paper that reported a

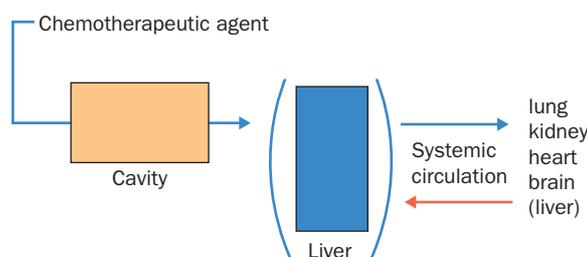


Figure 1. The fundamental goal of intraperitoneal chemotherapy is to increase exposure of the contents of the peritoneal cavity while reducing systemic toxic effects.

highly provocative pharmacokinetic rationale for the regional treatment of ovarian cancer.<sup>3</sup> This analysis, which took into consideration the natural history of ovarian cancer, anatomical and physiological characteristics of the peritoneal cavity and the liver, and the pharmacology of selected cytotoxic agents, suggested that direct intraperitoneal drug delivery could result in a profound increase in the exposure of the cavity to certain antineoplastic drugs, while reducing systemic exposure and toxic effects.<sup>4</sup> On the basis of these considerations, we can define the ideal antineoplastic agent, which could be examined for potential efficacy in clinical trials and, eventually in standard clinical practice (panel 1).

After that paper was published, several drugs were evaluated in phase I clinical trials, and initial predictions made with mathematical modelling proved to be remarkably accurate.<sup>5–13</sup> Differences in drug exposure of up to 1000 times were observed (both in terms of peak concentration and the area under the curve on a concentration versus time plot) between the peritoneal cavity and the systemic compartment after intraperitoneal drug delivery (table 1).<sup>5–13</sup>

Despite this impressive evidence of the potential for improved concentration-dependent cytotoxicity resulting in improved therapeutic efficacy,<sup>4</sup> several practical and theoretical concerns have been raised regarding the clinical usefulness of this route of drug delivery (panel 2).

The main problem with regional antineoplastic therapy is probably the limited depth of penetration of drugs directly

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into the tumour (or normal tissues) by free-surface diffusion. Any theoretical benefit associated with intraperitoneal treatment, beyond that achieved by delivery of the agent through capillary flow, will be due to this process. Experimental<sup>14–18</sup> and clinical data<sup>19–22</sup> support the conclusion that the high concentrations of drugs observed after delivery directly into the peritoneal cavity will only be relevant for patients with microscopic disease or very small volume macroscopic cancer—eg, largest residual mass less than 5.1 cm in diameter.

### Phase II trials of ovarian cancer

Intraperitoneal chemotherapy has been most thoroughly investigated in ovarian cancer, largely because of the anatomical distribution and overall inherent chemosensitivity of the disease. Thus, cisplatin, considered in the 1980s to be the single most important drug in the management of ovarian cancer, is the antineoplastic agent most extensively studied in this route of drug delivery.

Several phase I trials showed that it was possible to administer cisplatin intraperitoneally with minimum or no abdominal discomfort.<sup>6,7</sup> Furthermore, surgical procedures carried out after regional cisplatin delivery showed limited adhesion formation, suggesting the drug was not particularly irritating to the cells lining the peritoneal cavity. Pharmacokinetic analysis confirmed an approximately 10–20-fold advantage for exposure of the peritoneal cavity (both peak concentrations and area under the curve) compared with the systemic compartment after intraperitoneal administration of cisplatin.<sup>6,7</sup>

The dose-limiting toxic effects of regional cisplatin delivery were shown to be systemic rather than local side-effects—eg, nephrotoxicity, neurotoxicity, emesis. These data led to the hypothesis that exposure of tumour tissue to cisplatin through capillary flow should not be impaired after intraperitoneal administration. Pharmacokinetic analysis supported this conclusion as substantial concentrations of active cisplatin in the systemic compartment were reported after regional treatment.

Thus, when trials examining the potential efficacy of intraperitoneal cisplatin delivery in ovarian cancer began, investigators argued that the tumour should be exposed to the same concentration of drug as if the agent had been delivered intravenously. Theoretically, such concentrations

#### Panel 1. The ideal antineoplastic agent for intraperitoneal therapy

- Documented activity in the malignant disease to be treated
- Experimental or clinical evidence for concentration-dependent cytotoxicity of the agent against the malignant disease to be treated
- Not toxic to the peritoneal lining with regional delivery
- Slow exit from the peritoneal cavity and rapid clearance from the systemic circulation (increasing the pharmacokinetic advantage associated with regional delivery)
- Significant and rapid hepatic metabolism to a non-toxic metabolite (increasing the pharmacokinetic advantage associated with regional delivery)

would produce the added benefit associated with the high local concentrations of cisplatin within the peritoneal cavity.<sup>6</sup>

During the past 15 years, several phase II trials of intraperitoneal cisplatin as a second-line therapeutic strategy in ovarian cancer have been reported—responses have been documented through surgical reassessments after the completion of the regional treatment.<sup>19,21,23,24</sup> These studies clearly showed it was possible to produce objective responses in women who had failed to achieve this clinical state with systemic delivery, and reported surgically documented complete responses after the regional delivery of several antineoplastic agents, particularly cisplatin. The studies did however report that this strategy is only a rational consideration for patients with microscopic disease or tumours smaller than 0.5 cm in diameter. Long-term disease-free survival was observed in a subset of patients after regional delivery, but the absence of randomised controlled trials prevents any conclusion being drawn from the efficacy of this strategy compared with systemic delivery. There is no evidence from these phase II trials that the high concentrations of cytotoxic drug achievable with regional delivery can overcome the major inherent chemoresistance reported with systemic delivery.

The intraperitoneal delivery of other antineoplastic agents, both cytotoxic and immunological, have been investigated in phase I and II clinical trials for safety, pharmacology, and efficacy.<sup>8–11,13,22,25,26–30</sup> Two agents have produced good results. Carboplatin shows a pharmacokinetic advantage of 10–20-fold when delivered intraperitoneally (similar to that of cisplatin),<sup>8,9</sup> and has limited local toxic effects. Thus, as with cisplatin, the dose limiting side-effects of intraperitoneal carboplatin are due to systemic drug exposure (principally bone-marrow suppression). Limited phase II experience has confirmed the cytotoxic potential of intraperitoneal carboplatin in women with ovarian cancer.<sup>29,30</sup>

Paclitaxel exhibits a profound pharmacokinetic advantage after regional delivery (1000 times higher than systemic therapy).<sup>10,11</sup> However, in sharp contrast to the platinum, local toxic effects—eg, abdominal pain—are the dose limiting side-effects, leading to a reduced concentration of systemic exposure compared with intravenous therapy. These data suggest that optimum use of paclitaxel might comprise intravenous and intraperitoneal delivery of the drug.

A phase II trial of single-agent intraperitoneal paclitaxel as second-line therapy for ovarian cancer showed a surgically documented complete response rate of 61% in 28 women

**Table 1. Pharmacokinetic advantage of intraperitoneal delivery of selected antineoplastic drugs**

Agent	Ratio of peritoneal cavity to systemic compartment	
	Peak concentration	Total concentration*
Cisplatin	20	12
Carboplatin		18
Paclitaxel	1000	1000
Doxorubicin	470	
Mitoxantrone		1400
Melphalan	93	65
Methotrexate	92	
5-fluorouracil	300	360

\*Area under the curve for a concentration versus time plot.

**Panel 2. Practical and theoretical concerns about intraperitoneal chemotherapy**

- Unique toxic effects associated with local delivery—eg, abdominal pain, bowel perforation, infection, and obstruction
- Added time, inconvenience, and cost associated with the specific requirements of regional delivery—eg, catheter placement
- Adequacy of drug distribution throughout the entire peritoneal cavity
- Limited direct penetration of drugs into tumour or normal tissue
- Decrease in the delivery of drug to the tumour by capillary flow (through the systemic circulation) after regional delivery

with microscopic residual disease; only 1 of 31 patients (3%) with macroscopic cancer within the peritoneal cavity achieved this response.<sup>22</sup> This experience emphasises the limited direct penetration of cytotoxic agents into tumour tissue. Minimum concentrations of paclitaxel reached the tumour through the systemic compartment, thus relying almost exclusively on high local tumour–drug interactions for any observed biological effect.

**Survival in ovarian cancer**

Despite extensive phase II experience with intraperitoneal cisplatin-based chemotherapy in ovarian cancer, no randomised trials have directly compared this management approach with systemic drug delivery. Thus, it is not possible to draw any definitive conclusions about the overall clinical usefulness of this strategy in women with very small volume or microscopic residual disease. Hopefully, one of the large co-operative groups involved in the management of ovarian cancer will eventually carry out such a trial.

However, several institutions have reported long-term disease-free and overall survival (more than 4–5 years) with second-line regional treatment in this clinical setting.<sup>31–34</sup> Whether this outcome is due to a positive effect of treatment or simply represents the natural progression of disease in patients with favourable clinical characteristics has yet to be defined.

Barakat and colleagues have provided support for the concept that the delivery of several courses of intraperitoneal cisplatin to women with advanced ovarian cancer who achieve a surgically defined complete response decreases the risk of disease-progression.<sup>35</sup> They reported a substantially lower rate of relapse in patients who received three courses of intraperitoneal cisplatin and etoposide than in women who did not receive any further treatment after surgery, despite the fact that the latter group had more favourable clinical characteristics (higher percentage of patients with stage 2 than stage 3 disease and lower percentage of patients with suboptimum residual disease before first-line systemic chemotherapy). However, randomised trials are the only way to fully appraise intraperitoneal therapy as a consolidation strategy in ovarian cancer.

**Intraperitoneal chemotherapy as first-line treatment**

In contrast to second-line treatment of ovarian cancer, three well-designed randomised trials of cisplatin-based intraperitoneal therapy in the management of ovarian cancer have been reported (table 2).

The Southwest Oncology Group and Gynecologic Oncology Group compared intravenous cisplatin with intraperitoneal cisplatin in women with stage 3 ovarian cancer (largest residual tumour mass less than 2 cm in diameter) who had undergone initial surgical cytoreduction.<sup>36</sup> All the patients in the study also received intravenous cyclophosphamide. The trial reported a significant improvement in overall survival with intraperitoneal cisplatin (49 months vs 41 months, p=0.02). Furthermore, patients treated by the intraperitoneal route also experienced less toxic effects (neutropenia and tinnitus), probably because of reduced exposure of normal tissue to cisplatin with regional treatment.

Another trial by the Gynecologic Oncology Group compared intravenous cisplatin and intravenous paclitaxel with intraperitoneal cisplatin plus intravenous paclitaxel in women with stage 3 ovarian cancer whose largest residual tumour mass was less than 1 cm after surgery.<sup>37</sup> In the intraperitoneal group, patients also received two courses of moderately high-dose carboplatin, designed to debulk any residual tumour masses before the delivery of intraperitoneal cisplatin. This initial high-dose intravenous chemotherapy was given to optimise the opportunity to observe a benefit (presumably with smaller volume residual disease after intravenous treatment) from the increased tumour–drug interactions.<sup>38</sup>

However, the two initial courses of intravenous carboplatin proved to be excessively toxic (principally thrombocytopenia) and almost 20% of patients subsequently only received two courses or less of intraperitoneal cisplatin. Despite this setback, patients randomly assigned to receive intraperitoneal cisplatin showed a significant improvement in progression-free survival (28 months vs 22 months, p=0.01) and an 11-month increase in overall survival (63 months vs 52 months, p=0.05) compared with women receiving all of their therapy by the intravenous route.

Finally, a third randomised trial by the same group compared a standard intravenous chemotherapy regimen of cisplatin and paclitaxel with an experimental regimen of combined intravenous paclitaxel and intraperitoneal cisplatin and paclitaxel. A preliminary analysis of this study shows an improvement in progression-free survival associated with intraperitoneal administration (relative risk of recurrence 0.73 in favour of intraperitoneal treatment), but as yet, information on overall survival is premature.<sup>39</sup> A final report of the study, which includes regional

**Table 2. First-line intraperitoneal chemotherapy: risk hazard ratios in favour of regional drug delivery**

Regimen	Progression-free survival	Overall survival	Ref
IP cisplatin vs IV cisplatin (plus IV cyclophosphamide)	..	0.76	36
IP cisplatin vs IV cisplatin (plus IV paclitaxel)	0.78	0.81	37
IP cisplatin plus IV and IP paclitaxel vs IV cisplatin/paclitaxel	0.73	..	39

IP, intraperitoneal; IV, intravenous

treatment with the most active class of agents in ovarian cancer (cisplatin) and a drug that takes maximum advantage of the pharmacology associated with intraperitoneal cavity delivery (paclitaxel), is anticipated with considerable interest.

### Future role of intraperitoneal chemotherapy in ovarian cancer

Despite the effect of initial intraperitoneal chemotherapy on progression-free and overall survival in patients with small-volume residual advanced ovarian cancer, very few clinicians employ this management strategy other than in the trial setting.

There are several reasons for this apparent unwillingness. First, there has been concern that the added morbidity associated with regional drug delivery—eg, abdominal pain, infection, and bowel obstruction—and the time, effort, and cost of such treatment cannot be justified. However, this conclusion is not really supported by data from the randomised trials, which suggested that increased morbidity specifically associated with intraperitoneal drug administration, as opposed to the systemic effects of the antineoplastic drug itself, was quite modest in severity.<sup>36,37,39</sup>

In fact, it would be fair to state that these trials did not show any evidence for an increase in serious treatment-related morbidity or mortality. However, there is a learning curve associated with placement of indwelling intraperitoneal catheters (semi-permanent surgically-implanted devices or percutaneous insertion with each treatment cycle), as well with the management of any complications.<sup>40,41</sup> The early randomised trials would have shown the highest incidence of treatment-related morbidity, if such toxic effects actually existed. However, these trials did not report any serious problems associated with regional drug delivery, and included treatment in the community as well as in academic clinical settings. The use of semi-permanent indwelling intraperitoneal catheters to administer the therapy seems improve the ease of drug instillation and is more convenient for the patient (figure 2).

Second, there has been concern that clinicians are currently unwilling to use cisplatin, by either the intraperitoneal or intravenous routes, because of the superiority of carboplatin with regards to systemic toxic effects—eg, less nausea, vomiting, nephrotoxicity, and neurotoxicity.<sup>42,43</sup> Therefore, given the choice of carboplatin-based systemic chemotherapy or cisplatin-based intraperitoneal chemotherapy, physicians will probably elect to use intravenous treatment, despite the significant improvement in survival associated with the use of intraperitoneal cisplatin in this malignant disease.

Thus, it would be appropriate to study the feasibility and effectiveness of delivering intraperitoneal carboplatin, rather than cisplatin, to women with small-volume, residual, advanced ovarian cancer after surgical cytoreduction. Phase I data support the safety and pharmacokinetic advantage associated with this approach.<sup>8,9</sup> Also, limited phase II experience has confirmed the cytotoxic potential of intraperitoneal carboplatin as a second-line treatment of ovarian cancer.<sup>29,30,44</sup>

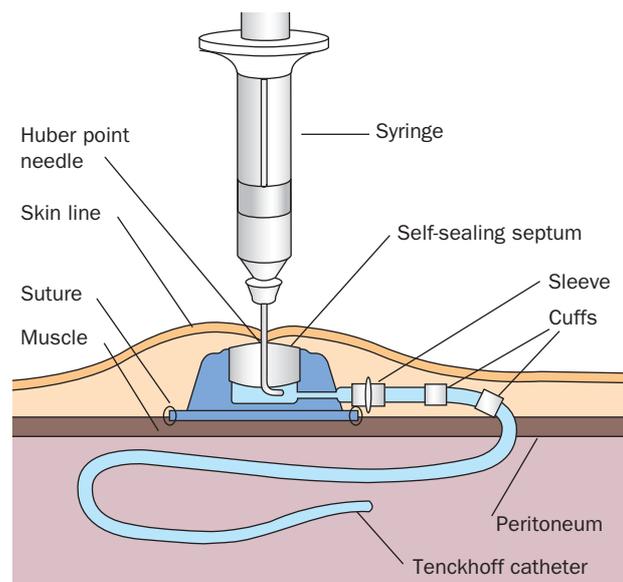


Figure 2. A semi-permanent indwelling intraperitoneal catheter delivery system.

Preclinical evaluation and limited data from non-randomised clinical trials suggest the possibility that direct uptake of carboplatin with intraperitoneal delivery (after free-surface diffusion) may be less than that which occurs with cisplatin.<sup>45,46</sup> Whether there is any clinical relevance to these concerns can only be assessed by a randomised phase III trial comparing the two drugs by the intraperitoneal route. However, it is virtually certain that intraperitoneal chemotherapy as a first-line treatment in ovarian cancer would be far more acceptable to both physicians and patients if carboplatin was used instead of cisplatin, without sacrificing the effectiveness of such regional treatment.

An alternative strategy would be to examine a lower dose of cisplatin—eg, 50–75 mg/m<sup>2</sup> instead of 100 mg/m<sup>2</sup>—with the aim of reducing the anticipated systemic toxic effects. This modification would be worthy of investigation in a randomised trial.

### Other tumour types

The intraperitoneal administration of antineoplastic agents has been investigated in other tumour types that are principally confined to the peritoneal cavity, including gastrointestinal malignancies<sup>47–53</sup> and peritoneal mesothelioma.<sup>54–57</sup> For several reasons it has been even more difficult to define a role for intraperitoneal therapy in these tumours than for ovarian cancer.<sup>58</sup>

The pattern of metastatic spread of these diseases is generally different from that observed in ovarian cancer, with prominent and early involvement of the liver and retroperitoneal lymph nodes—areas which would not be expected to experience any benefit from high intraperitoneal drug concentrations. Moreover, the pattern of local spread, with large tumour masses rather than smaller diffuse nodules, would be less conducive to direct exposure of intraperitoneal tumour tissue to the instilled treatment volume. The cytotoxic potential of current chemotherapeutic

agents is far less in this group of malignant diseases than in ovarian cancer. Surgical cytoreduction is a rare treatment in these malignant states but such surgery is common in the treatment of ovarian cancer and aids the optimum use of regional antineoplastic drug delivery.

Finally, some tumours in the peritoneal cavity have a prolonged natural history, despite their tendency to diffusely spread throughout the compartment. For example, metastatic carcinoma of the appendix may involve the whole peritoneal cavity resulting in significant symptoms. Patients with this condition, known as pseudomyxoma peritonei, may have a remarkably indolent disease course, lasting many years.<sup>59</sup> Surgical cytoreduction is likely to reduce the volume of cancer and the large quantities of non-malignant mucinous material secreted by the tumour, and can substantially improve patient comfort and perhaps even survival in this low-grade tumour.

However, if intraperitoneal chemotherapy was used alongside an aggressive attempt to remove all gross tumour bulk, it would be very difficult to specifically determine the effects of regional therapy (with respect to disease-free and overall survival) because of the long natural history of this relatively indolent malignant disease. Thus, it is vital that randomised trials be done in these clinical settings to conclude whether intraperitoneal cytotoxic drug administration offers any benefit over that achieved by surgical cytoreduction alone.

### Micrometastatic cancer in the liver

Experimental and clinical data have definitively shown that macroscopic metastatic disease in the liver receives blood from the hepatic arterial circulation. However, preclinical data show that a substantial portion of the capillary system associated with the first microscopic cancerous deposits in the liver comes from the portal vein.<sup>60,61</sup> Thus, since drug uptake from the peritoneal cavity largely occurs through the portal circulation, intraperitoneal antineoplastic therapy may be an effective adjuvant treatment for certain gastrointestinal cancers that are associated with a high risk of dissemination to both the cavity and the liver—eg, high-grade localised colon cancer with serosal or nodal involvement.

Randomised trials of the clinical relevance of this hypothesis have reached conflicting conclusions, reflecting the complexity of metastatic spread in this group of malignant diseases, the substantial heterogeneity within single cancer types, and the limited effectiveness of current chemotherapy options.<sup>47–50</sup> At this point, it is reasonable to conclude that intraperitoneal chemotherapy as an adjuvant treatment of gastrointestinal malignant disease remains within the realm of clinical investigation.

### Biological and immunological agents

As with traditional chemotherapy drugs, the regional delivery of biological or immunological agents may increase tumour–drug interactions, enhance the opportunity for concentration-dependent cytotoxicity, and improve outcome. Intraperitoneal administration has the potential to directly activate local immunoregulatory mechanisms—eg,

### Search strategy and selection criteria

Medline was searched for relevant articles using the terms “intraperitoneal drug delivery”, “regional cancer chemotherapy”, and “ovarian cancer”.

natural killer cells—indirectly leading to immune-mediated death of tumour cells.<sup>62</sup>

Several biological agents have been explored for a possible role in this clinical setting, including interferon  $\alpha$ , interferon  $\gamma$ , interleukin 2, and tumour necrosis factor.<sup>26–28,62</sup> Phase I data have defined the pharmacokinetic advantage of this approach and the potential for toxic effects, including local effects (eg, abdominal pain) and systemic effects (eg, fever and chills). In addition, other studies have confirmed the stimulation of immunomodulatory cells in the peritoneal cavity with regional treatment, and objective responses (as defined clinically and surgically) have been seen.

However, with a few exceptions, there are no randomised phase III trials of this management strategy in ovarian cancer or non-ovarian malignant diseases. Thus, a role for the intraperitoneal administration of biological agents other than in clinical trials setting remains to be defined.

### Conflict of interest

None declared.

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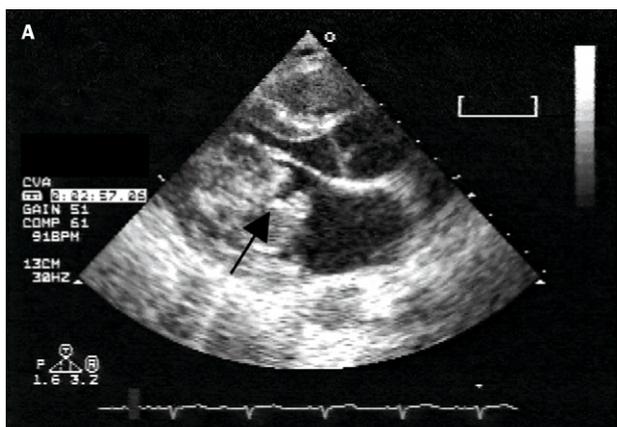
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## Clinical Picture

### Primary cardiac synovial sarcoma

Teresa T McGilbray and Thomas K Schulz



A 30-year-old man presented with a witnessed seizure and loss of consciousness. An MR image of the brain showed multiple embolic infarcts and a 2 dimensional echocardiogram showed a large mitral-valve mass (figure a). The patient underwent open-heart surgery to remove what was thought to be a myxoma. However, a pathological examination of the removed tissue identified a biphasic synovial sarcoma (figure b). This was confirmed by identification of a chromosomal translocation, t(X;18), that

associates with more than 90% of all synovial sarcomas. Distinguishing between a synovial sarcoma and a primary cardiac mesothelioma of the heart can be difficult and it is important to confirm the t(X;18) translocation to verify the diagnosis. Synovial sarcomas usually occur in the par-articular regions of the extremities; an occurrence distal to the synovial-lined spaces is rare and only a limited number of cases have been documented. The patient survived surgery and received follow-up ifosfamide-based chemotherapy.

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