young patients. However, just like the other randomised trials comparing BCT and mastectomy, the small number of patients in the youngest age group did not allow us to find the answer to this question. We therefore agree with Arriagada and colleagues [1] that more data are needed to determine the safety of breast conservation in patients ≤35 years old, and ways to reduce their risk of local recurrence. It is probable that future studies will reveal (genetic) factors that predict local recurrence more accurately. Another way to reduce the high risk of local recurrence in younger patients is to apply more effective treatment strategies. For instance, one might consider changing the radiation dose or techniques, or including one course of peri-operative chemotherapy, which has been demonstrated to reduce the risk of loco-regional recurrence by 50% in node-negative premenopausal patients <43 years of age [3].

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Acute dyspnea due to right phrenic palsy during infusional chemotherapy

Central venous catheters (CVCs) are widely used in cancer patients, particularly for continuous infusional chemotherapy. CVCs have many complications, but with the exception of catheter-related bloodstream infections and thrombosis, most are rare. We describe a clinical case of acute dyspnea due to unexpected right phrenic nerve injury during 5-fluorouracil (5-FU) continuous infusion plus cisplatin and epirubicin chemotherapy (ECF schedule).

A 50-year-old woman had developed a locally advanced breast carcinoma (cT4dN2M0). A port, attached to an open-ended catheter tubing, was implanted on the right side in order to safely administer primary chemotherapy according to ECF schedule (5-FU 200 mg/m^2 administered as continuous infusion and epirubicin 50 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks). The procedure appeared without acute complication such as haematoma or haemorrhage. A subsequent chest X-ray confirmed the correct positioning of the catheter and diaphragm. From July to August 2002 two cycles were administered. During the third cycle the patient presented with acute dyspnea and right shoulder pain. A chest radiography documented a raised right hemidiaphragm; a chest CT scan was negative for mediastinal involvement and thrombosis of the superior vena cava. The echocardiography evaluation and the radionuclide lung scanning was negative for pulmonary embolism. The electroneurography of the phrenic and peripheral nerves, bilaterally, showed clear right phrenic nerve injury concordant with axonal damage. Electroneurography of the peripheral nerve showed a normal sensory-motor conduction, a finding that does not support the hypothesis of a peripheral neurotoxicity. The chemotherapy was stopped and the patient underwent a radical mastectomy followed by adjuvant chemotherapy. The patient is still alive and is receiving palliative chemotherapy with trastuzumab and vinorelbine. There have been no respiratory complications during follow-up despite the hemidiaphragm remaining paralysed 12 months after removal of the catheter.

To our knowledge, this is the first report of such a phenomenon in patients with breast cancer during ECF chemotherapy. A previous large trial with ECF schedule did not report such a phenomenon [1].

Our clinical case differs from other similar clinical conditions reported in the literature. Reeves et al. described a permanent paralysis of the right phrenic nerve associated with thrombosis of the superior vena cava [2]. Munzone et al. hypothesized that vinorelbine [3], as previously reported *in vitro* [4], could have damaged the permeability of the endothelial barrier near the catheter tip, favouring the occurrence of the right phrenic nerve injury due to a chemical vasa nervorum vasculitis.

Nevertheless, phrenic nerve damage is a rare complication of central venous catheterization and the aetiology is not entirely understood. This type of complication can occur during or shortly after the insertion procedure and is generally due to direct trauma, local haematoma or the use of local anaesthesia, as the phrenic nerve travels in close proximity to the veins usually used for catheterization. When the 'acute' nerve damage is due to local haematoma or anaesthesia it may be transient and even resolve in a few hours or days [5]. On the contrary, delayed damage may be irreversible. According to Mir et al. this type of complication has been reported not only in patients undergoing chemotherapy but also in patients with long-term subclavian catheter used only for haemodialysis [6]. In addition, in delayed nerve damage it has been suggested that a catheter-related inflammatory reaction may be the cause of the phrenic damage, independent of the chemotherapy infusion.

In our clinical case, the diaphragmatic paralysis appears to be permanent, showing no improvement 12 months after catheter removal. The electroneurography of the bilateral phrenic and peripheral nerves is not able to exclude that the phrenic nerve damage may be due to a catheter-related inflammatory reaction, even if the

onset during continuous infusional chemotherapy suggests that chemotherapy could play a role.

Since the use of an implanted catheter for infusional chemotherapy has increased dramatically in the past decade in cancer patients, and because of the different clinical features of the reported clinical cases, we strongly recommend careful monitoring of any shoulder pain occurring in patients during continuous infusion of chemotherapy, irrespective of the type of chemotherapy and thrombosis formation.

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Extrathymic malignancies in patients with thymoma

Thymomas are often associated with autoimmune disorders, of which myasthenia gravis (MG) is by far the most common; moreover, an increased incidence of extrathymic tumors has been reported in these patients [1–3].

A center for MG at the Catholic University, Rome, has been active for >20 years; since 1996, clinical follow-up has also included thymoma patients without MG. We have compared thymoma cases both with and without MG in order to look for possible differences in the rate of additional malignancies.

We evaluated 107 patients operated on for thymoma in the period 1996–2002, with ≥6-months follow-up after surgery. Tumor histology was classified according to the World Health Organization (WHO) classification [4]. The presence of autoimmune diseases other than MG and immunosuppressive and adjuvant treatments were recorded. Extrathymic malignancies were diagnosed on the basis of chart review, periodic patient examinations and analysis of the hospital tumor registry. Statistical analysis was performed using the chi-square test with Yates correction and Student's *t*-test.

Table 1. Extrathymic tumors in thymoma patients

Tumors	Thymoma patients	
	MG (n = 75)	non-MG (n = 32)
Skin tumors		
Basaloma	2	–
Spinalioma	–	1
Keratoacantoma	1	–
Adenocarcinomas		
Breast	–	1[b]
Colon	–	1
Lung	1[a]	1
Prostate	1	1
Renal	–	1
Thyroid papillary tumor	1	1[b]
Bladder carcinoma	–	1
Meningioma	–	1
Neurinoma	1[a]	–

[a,b]Associated in the same patient.
MG, myasthenia gravis.

Thymoma was associated with MG in 75 patients (34 male/41 female), with a mean age at thymomectomy of 52 years (range 15–70); thymoma was not associated with MG in 32 subjects (19 male/13 female), mean age 56 years (range 18–78). Mean follow-up was 45 (range 8–85) and 43 months (range 6–88) in MG and non-MG patients, respectively. All thymoma histological subtypes were found in non-MG patients; type C thymic tumors were absent in the MG series. Adjuvant treatment consisted of radiotherapy (25 MG and five non-MG patients), cisplatin-based chemotherapy (eight MG and three non-MG patients) and both radio- and chemotherapy (five MG and three non-MG patients). Other autoimmune disorders were diagnosed in 12 of 75 (16%) MG patients and in 6 of 32 (19%) non-MG subjects. Sixty-three MG patients received immunosuppressive therapy (in most cases prednisone plus azathioprine); three non-MG subjects were treated with steroids because of their autoimmune diseases (polymyositis, systemic lupus erythematosus, pemphigus).

Additional tumors were noted in six of 75 MG (8%) and in eight of 32 non-MG subjects (25%) (P = 0.038). One patient in each group had two extra-thymic malignancies. These data are shown in Table 1. Eight cancers were diagnosed at the same time as thymoma, three occurred before and five after thymomectomy. No preferential association with any thymoma subtype was observed. Of those patients with extrathymic tumors, three non-MG cases were also affected by autoimmune diseases, four MG and two non-MG subjects were receiving immunosuppressive therapy; adjuvant treatment had been administered to three MG