normal range. Chemotherapy was stopped after two courses because of metastatic progression in the liver (invading more than 50% of the liver). Uric acid was still elevated (700 μmol/l) without any specific treatment, and phosphataemia was 1.38 mmol/l. Other biological values were normal except a cholestasis with total bilirubinaemia slightly increased up to 25 μM/l and LDH to 1000 UI/l. We decided to treat this patient with irinotecan (compassionate use, Laboratoires Bellon). She received a reduced dose of 300 mg/m^2 because of the cholestasis. At day 8, she was admitted for a profound general deterioration. Laboratory exploration showed severe metabolic anomalies consisting of a major uric acid increase up to 1816 μmol/l, hyperphosphataemia (2.68 mmol/l) with hypocalcaemia (2.0 mmol/l), hyperkalaemia (6.0 mmol/l) with bicarbonates at 21 mmol/l, and renal failure with serum creatinine at 200 μM/l. LDH was 3600 UI/l. Despite forced diuresis, urine alkalinisation and uricolytic therapy, the patient died 48 h later due to renal failure with anuria.

To our knowledge, TLS has never been described as a complication of metastatic colorectal cancer [1]. However, this patient had many common features described in TLS-associated malignancies: bulky tumour, rapid growth, evidence of spontaneous TLS [2]. The rapid progression of the disease and the moderate increase of the lysis with 5-FU reflects the inactivity of this drug. Irinotecan (CPT-11) is a new cytotoxic agent, an inhibitor of the DNA enzyme topoisomerase I, which is effective against advanced and metastatic colorectal cancer, with an 18% response rate in first-line therapy or in tumour resistant to 5-FU [3]. The acute TLS observed in this patient confirms the activity of this agent in a tumour resistant to 5-FU. The principal adverse events of CPT-11 are neutropenia and delayed diarrhoea of secretory mechanism, and are both dose related. None of these effects were observed in our patient. The acute TLS described here is a previously unreported adverse event of CPT-11. Renal failure was probably due to hyperuricaemia combined with hyperphosphataemia. SN 38, the active metabolite of irinotecan, is mainly excreted in the bile and a renal toxicity of irinotecan has never been previously described [4]. This case illustrates that administration of irinotecan for bulky tumours of colorectal origin with rapid doubling time may induce an acute TLS which necessitates frequent laboratory monitoring and prevention by abundant hydration and hypouricaemic treatment.

1. Drakos P, Bar-Ziv J, Catane R. Tumor lysis syndrome in nonhematologic malignancies: report of a case and review of the literature. *Am J Clin Oncol* 1994, **17**, 502–505.
2. Barton J. Tumor lysis syndrome in nonhematopoietic neoplasms. *Cancer* 1989, **64**, 738–740.
3. Armand JP, Ducreux M, Mahjoubi M, *et al.* CPT-11 (Irinotecan) in the treatment of colorectal cancer. *Eur J Cancer* 1995, **31A**, 1283–1287.
4. Chabot G, Abigerges D, Catimel G, *et al.* Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. *Ann Oncol* 1995, **6**, 141–151.

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Major Interactions Between Radiation Therapy and Systemic Sclerosis: Is There an Optimal Treatment?*

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SYSTEMIC SCLEROSIS (SSc) is a collagen vascular disease characterised by fibrosis, resembling that observed in late radiation damage. An unusually high incidence of complications after radiation therapy (RT) has recently been reported in patients with SSc [1–6]. In these series an excessively severe fibrosis, extending beyond the irradiated fields, rapidly occurred and caused death in a third of patients. However, RT was delivered after surgical removal of the tumour and tumour regression in relation to RT could not be evaluated. We describe here fast and striking tumour regression after reduced RT dose for malignant tumours in 3 patients with severe SSc.

3 patients who had had evolutive SSc for 8–16 years developed inoperable locally advanced cancer and were treated by RT. A total dose of 40–45 Gy in 6 weeks and fraction of 1.8 Gy was delivered with a 4.5 MV photon beam to the tumour. None of the patients was given chemotherapy or a radiosensitiser.

Patient 1

A 54-year-old man with SSc including interstitial pneumonitis and myocarditis presented with T_3 N_2 M_0 epidermoid lung cancer. He received 40 Gy of thoracic RT over 6 weeks. Immediate clinical RT tolerance was excellent, but a 15% decrease in lung diffusing capacity was observed. Evaluated on CT scan, tumour volume reduced by half after a 20 Gy given-dose and by 85% at the end of treatment, thus allowing subsequent surgery. Right pneumonectomy with node dissection was performed 6 weeks later. Pathological examination of the surgical specimen showed a large volume of necrosis without viable tumour cells. The patient died suddenly of respiratory distress syndrome, three days after surgery. Post mortem examination indicated lethal lung fibrosis with haemorrhagic alveolitis compatible with SSc.

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Patients 2 and 3

Two 72-year-old women were treated by RT only for T_3 N_0 M_0 epidermoid carcinoma of the anorectal region. A four-field box technique was used to deliver 20–22 Gy to the pelvis and inguinal nodes, followed by a 20–22 Gy tumour boost. Marked acute side-effects were observed in both cases, with severe transient diarrhoea and anal incontinence. Digital examination showed 50% tumour reduction half way through the treatment and complete clinical remission at the end, confirmed by subsequent biopsies.

In 1 patient, several complications occurred rapidly in the irradiated volume, with bilateral femoral neck fractures at 3 weeks and 5 months, thrombosis of the right femoral artery at 8 months and anal necrosis initiated by a control biopsy. Anal healing was obtained by local steroid instillations and one year oral pentoxifyllin treatment. With a 42 month follow-up, the patient remained free of tumour. In the other patient, a limited local recurrence occurred 1 year after RT. The patient was successfully treated by conservative surgery plus 20 Gy preoperative brachytherapy, but developed a minimal postoperative rectovaginal fistula one month later. She was free of disease at 18 months.

Few data on the clinical effects of RT in patients with SSc are available in the literature. The published series include 12 patients with previous, concomitant or delayed SSc, who were treated by RT for malignant tumours [1–6]. In most patients, surgical removal of the tumour did not allow the evaluation of tumour regression during RT and the authors mentioned nothing about the long-term local tumour control. Nine of these patients, who received total doses of 50–75 Gy, developed very severe fibrosis overlapping the irradiated fields, with toxic death in 4 cases. No late complications were observed in the 3 remaining patients after RT, consisting of a maximum 40 Gy external beam.

Taking into account this major toxicity, we treated 3 cancer patients presenting with severe SSc with deliberately reduced RT total dose, ranging from the usual 65 Gy to 40 Gy. Surprisingly, the tumours regressed rapidly during RT and the patients were in complete clinical remission after a total dose of 40 Gy which is usually far from optimal in the treatment of epidermoid carcinomas. This remission was confirmed by the histology of tumour-free biopsy specimens. The large reduction in the RT dose did not appear to be detrimental to local tumour control. To our knowledge, this clinical observation has not been described before. However, despite the reduction in the radiation dose, we were unable to avoid one toxic death and severe side-effects, which developed in the visceral organs included in the irradiated volume. Nevertheless, we did not observe either cutaneous reactions in the irradiated area, or fibrosis spreading out of the RT portals. In addition, the SSc did not worsen in the 2 patients still alive.

The pathogenesis of the interactions between RT and SSc is not known. However, the results of biological studies suggest several plausible explanations for the delayed RT-related complications in SSc patients [7]. Endothelial cells and fibroblasts are involved histologically in both early radiation-induced fibrosis (RIF) [8] and SSc [9]. In both disorders, fibrosis is characterised by excessive cell proliferation and extracellular matrix deposition. The level of transforming growth factor β (TGFβ) was found to be abnormally high in RIF [10] and SSc [11] and was considered the main factor in the initiation of fibrosis and its long-term cellular activation. Further, additional signals of healing such as biopsy, surgery or local infection worsened the late effects of radiation.

Finally, stromal tumour fibroblasts could play a key role in tumour cell sensitivity to radiation, as observed in psoriasis. On the basis of *in vitro* assays, Gery and Little recently demonstrated the modulation of tumour cell radiosensitivity by an additional fibroblastic supernatant [12]. Sclerodermal fibroblasts might interfere with the paracrine communication between epithelial tumour cells and connective cells. Such interference might constitute the mechanism of the rapid and complete control of advanced tumours obtained here with a reduced RT dose.

In conclusion, if surgery is not possible for SSc patients, a reduction of a third in radiation dose and volume can be expected to permit control of locally advanced carcinomas without concomitant chemotherapy, and is mandatory to avoid lethal complications.

1. Fleck R, McNeese M, Ellerbroek N, *et al.* Consequences of breast irradiation in patients with pre-existing collagen vascular disease. *Int J Radiat Oncol Biol Phys* 1989, **17**, 829–833.
2. Varga J, Haustein U, Creech R, *et al.* Exaggerated radiation induced fibrosis in patients with systemic sclerosis. *JAMA* 1991, **265**, 3292–3295.
3. Abu-Shakra M, Lee P. Exaggerated fibrosis with systemic sclerosis (scleroderma) following radiation therapy. *J Rheumatol* 1993, **20**, 1601–1603.
4. Ross J, Hussey D, Mayr N, Davis C. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. *Cancer* 1993, **37**, 3744–3752.
5. Cooper S, Denham J. Progressive systemic sclerosis (diffuse scleroderma) and radiotherapy. *Br J Radiol* 1990, **63**, 804–805.
6. Roberston J, Clarke D, Pevzner M, Matter R. Breast conservation therapy. Severe breast fibrosis after radiation therapy in patients with collagen vascular disease. *Cancer* 1991, **68**, 502–508.
7. Delanian S. Pathophysiological aspects of radiation-induced fibrosis. *Bull Cancer (Radiother)* 1995, **82**, 88–93 (In French).
8. Lefaix J, Martin M, Tricaud Y, Daburon F. Muscular fibrosis induced after pig skin irradiation with single doses of Ir gamma rays. *Br J Radiol* 1993, **66**, 537–544.
9. Claman H, Giorno R, Seibold J. Endothelial and fibroblastic activation in scleroderma. *Arthritis Rheum* 1991, **34**, 1495–1501.
10. Martin M, Lefaix J, Pinton P, Crechet F, Daburon F. Temporal modulation of TGF b1 and b-actin gene expression in pig skin and muscular fibrosis after ionizing radiation. *Radiat Res* 1993, **134**, 63–70.
11. Smith E, Leroy E. A possible role for transforming growth factor-b in systemic sclerosis. *J Invest Dermatol* 1990, **95**, 125s–127s.
12. Gery B, Little J. Modulation of human tumour cell proliferation and radiosensitivity after contact with fibroblast supernatant. *Bull Cancer (Radiother)* 1993, **80**, 455 (In French).