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### Angiogenesis inhibition in high grade glioma

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# Chapter 6.

A gross pathology specimen of a segment of bowel, likely the small intestine, showing multiple perforations. Three red arrows point to the perforated sites. The bowel is yellowish-tan and appears thickened and inflamed. The perforations are visible as dark, irregular holes in the mucosal surface.

**Bowel perforation after radiotherapy  
in a patient receiving sorafenib**

## Bowel Perforation After Radiotherapy in a Patient Receiving Sorafenib

A 61-year-old woman was diagnosed with renal cell carcinoma (RCC, clear-cell type) and cutaneous metastases. As a firstline treatment she received sorafenib (BAY-43-9006, Nexavar; Bayer, West Haven, CT, and Onyx, Richmond, CA), 400 mg twice a day. A rapid regression of the cutaneous metastases was observed, but an magnetic resonance imaging (MRI) scan after four weeks of treatment revealed no change in the tumor in the right kidney. Grade 1 and 2 (National Cancer Institute Common Toxicity Criteria) toxicity was documented, in addition to hand-foot syndrome and mouth pain. Five weeks after the start of sorafenib treatment, the patient developed severe low back pain. MRI of the lumbar spine showed a lytic bone metastasis of the lumbar vertebra (L) 4, which was treated with palliative radiotherapy on L3-L5 (8 Gy, one fraction).<sup>1,2</sup> Sorafenib was stopped 2 days before radiotherapy to prevent radiosensitizing of the normal tissue. Sorafenib treatment was started again 3 days later. One week after radiotherapy the patient was admitted to our hospital suffering from abdominal pain, diarrhea, and dehydration. On physical examination she had no fever, her blood pressure was RR 90/60 mmHg, and her pulse rate was 120 beats per minute. Abdominal examination revealed signs of peritonitis. Laboratory tests showed leukocytosis ( $24.7 \times 10^9/L$ ) and renal failure (creatinin, 324 mol/L; urea, 37 mmol/L). She was therefore treated with intravenous fluids and antibiotics. Her clinical condition worsened rapidly and she died the next day. The autopsy revealed multiple perforations of the transverse and sigmoid colon with fecal peritonitis (Fig 1; arrows point to perforations). Biopsy specimens of the colon showed ischemic enteritis with radiation-effects and vascular changes with thrombus formation, but no evidence of tumor metastases. The primary kidney tumor

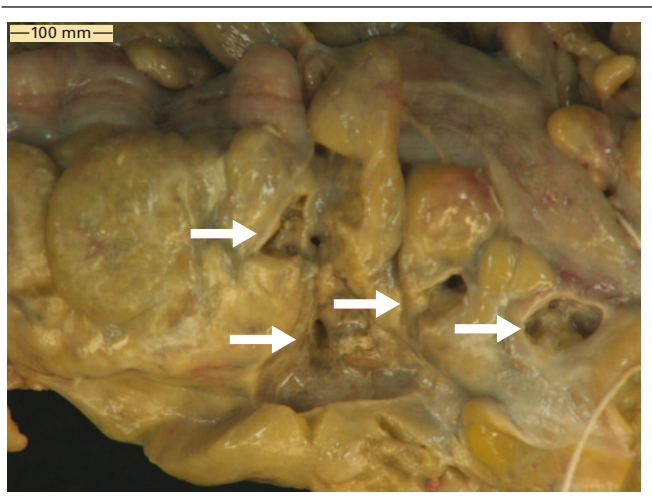


Fig 1.

demonstrated a clear-cell RCC with extensive sarcomatoid changes. The outcome for patients with metastatic RCC has been shown to improve considerably with the administration of sorafenib and sunitinib, both small molecules with angiogenesis inhibiting activity which act by blocking the signaling through vascular endothelial growth factors (VEGFs) receptor and the platelet-derived growth factor receptor.<sup>3,4</sup> In 75% of sporadic clear-cell RCC mutations are found in the von Hippel-Lindau gene. These mutations result in upregulation of hypoxia inducible factor 1- $\alpha$ , which binds to a variety of transcriptional cofactors that activate transcription of hypoxia-inducible genes, including VEGF.<sup>5</sup> Therefore, therapies such as sorafenib that block these pathways are a useful treatment for patients with sporadic clear-cell RCC. The adverse effects of sorafenib include fatigue, rash/desquamation, hand-foot skin reaction, pain, diarrhea, and hypertension.<sup>3</sup> Our patient showed a mixed response to sorafenib therapy. The cutaneous metastases disappeared during treatment, but the primary kidney tumor was not seen to regress by MRI. In addition, progressive complaints caused by the osteolytic metastasis in L4 suggested local tumor progression during the course of treatment. Pathologic examination of a pretreatment biopsy from a cutaneous metastasis showed a clear-cell carcinoma, without the sarcomatoid transformation observed in the primary kidney tumor. Although sarcomatoid differentiation of a clear-cell carcinoma seems to be an indicator of poor prognosis there have been no studies to link this type of tumor with sorafenib resistance.<sup>6</sup> The dramatic occurrence of multiple perforations in the sigmoid colon after radiotherapy suggests a causal relation with the given treatments. This causality was supported by the observation that the perforated sigmoid area was located in the anterior-posterior/posterior-anterior radiation fields of the osteolytic lesion in L4 (Fig 2; computed tomography with oral and intravenous contrast; red area received 100%, and green area received 90%, of irradiation). It is interesting to note that radiation-induced tissue damage is often characterized by vascular abnormalities and ischemia, as described in the colon specimen of this patient.

The normal bowel tolerance dose of radiation is in the order of 50 Gy in 25 fractions.<sup>7</sup> A single fraction of 8 Gy is biologically well below the tolerance dose. The incidence of sigmoid perforation caused by high-dose radiotherapy for cervical cancer is 0.6% with a range of between 3 and 98 months post-treatment.<sup>8</sup> No gut toxicity resulting from single-dose 8 Gy radiotherapy has been reported. Irradiation causes hypoxia and upregulation of VEGF, a growth factor involved in radio-resistance.<sup>9</sup> By inhibiting the activity of VEGF by receptor blockade, sorafenib can potentially act as a radiosensitizer. Several in vitro and in vivo studies have shown that combined treatment with such VEGF- or VEGF receptor-inhibitors with irradiation induces synergistic antitumor activity.<sup>10,11</sup> A radiosensitizing effect of VEGF pathway inhibition on cancer cells has also been described in several preclinical studies, though clinical data on sorafenib is limited.<sup>12-14</sup> In light of these reports, the high level bowel toxicity in our patient is surprising. Possibly the 2 day gap between the end of sorafenib treatment and the start of radiotherapy was too short. Since sorafenib has

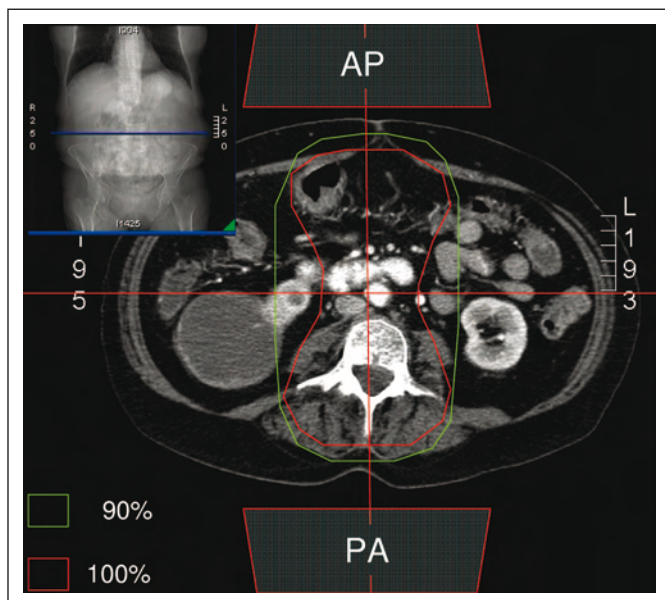


Fig 2.

an approximate half-life of 24 to 48 hours, there may have been residual sorafenib present during radiation treatment and thus normal tissue was still radiosensitized via sorafenib. This report describes a patient receiving sorafenib that developed a lumbar metastasis that required irradiation. She died of complications in the bowel—the area directly targeted by irradiation. In conclusion, this case provides evidence for potential oversensitization of normal tissue by sorafenib. Further studies combining antiangiogenic therapy with radiotherapy are warranted in order to further determine the efficacy and toxicity of combination therapy of sorafenib with radiation.

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest

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