

dose" by "fraction dose" or "dose per fraction," and the term "fractionation" by "fraction number." The recommended dose concept for "calca-neodynia" = "plantar or dorsal calcaneal spur" would then appear as follows: Single dose = fraction dose, 0.5–1.0 Gy; fractionation = fraction number, 2–3 times per week; total dose = total dose, 3–12 Gy. Recommended: Every 2 days 0.5–1.0 Gy \times 6 up to a maximum of 6.0 Gy total dose; in the case of slow response (application of) second series after 6–12 weeks.

It is important to note that in the clinical routine (single) fraction doses of 0.5 Gy or 1 Gy are not arbitrarily chosen, but instead intentionally applied by experienced radiation therapists. It was early clinically observed and recommended by von Pannewitz—an important German radiation therapist dealing with nonmalignant disorders—that early stages of inflammatory processes may respond much better to lower fraction doses of \leq 0.5 Gy applied 3–5 times per week for about 2–3 weeks than chronic inflammatory disorders, which may require fraction doses of 0.6–1.0 Gy applied only 2–3 times per week for about 2–3 weeks (3, 4). Thus, we may have to differentiate between acute ($<$ 4 weeks from symptom onset), subacute inflammatory processes (4 weeks to 6 months from symptom onset), and chronic inflammatory processes. As radiotherapy is usually applied as "a last resort" approach when failing other therapies, mostly a chronic inflammatory process is present and the concept would be 6 fractions of 1.0 Gy applied in 2–3 weekly fractions up to a total dose of 6 Gy. In case of persistent or incompletely regressed pain, a second radiotherapy series with the same dose concept would be applied up to a total dose of 12 Gy. The clinical outcomes of these different concepts for plantar fasciitis or achilodinia have been described in a prospective study (5).

In summary, the clinical background of the inflammatory disorder and the applied radiation dose concept have to match each other to obtain the best result for the individual patient.

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DETERMINATION OF TGF- β 1 PLASMA LEVELS: IN REGARD TO ANSCHER *ET AL.* (INT J RADIAT ONCOL BIOL PHYS 2003;56:988–995) AND DE JAEGER *ET AL.* (INT J RADIAT ONCOL BIOL PHYS 2004;58:1378–1387)

To the Editor: In patients with non-small-cell lung cancer, increasing radiotherapy (RT) dose improves eradication of intrathoracic disease, but increases the risk of side effects, especially radiation-induced lung injury. Many studies have been aimed at finding indices allowing the determination of the risk of treatment-related complications.

These indices include biologic factors and dosimetric parameters such as mean lung dose or the volume of lung receiving a threshold dose (e.g., 20 or 30 Gy). Among the biologic factors, interleukin-1 α and interleukin-6 would be early circulatory cytokine markers for radiation pneumonitis (1, 2). Transforming growth factor (TGF)- β 1 is another potential marker. As recently shown in a human study determining local concentrations of TGF- β 1 in the lung before, during, and after thoracic irradiation for lung cancer, TGF- β 1 may contribute to the process leading to radiation response in human lung tissue (3). Anscher and his team found that elevated TGF- β 1 plasma levels at the end of RT can identify patients at greater risk of

pulmonary complication associated with thoracic irradiation for lung cancer (4). They proposed to use TGF- β 1 plasma levels to assess the risk of treatment-related complications and consequently adjust the dose of radiotherapy. However, in a report published in the last issue of this journal, De Jaeger *et al.* failed to confirm that patients with increased TGF- β 1 levels at the end of RT are at higher risk for developing symptomatic radiation pneumonitis (5).

Possible reasons for discrepancy include the use of different criteria to define treatment related complications and differences in the way plasma is collected and processed to determine TGF- β 1 plasma levels. In humans, TGF- β 1 is mainly found in the platelets α -granules and can be released in plasma in response to platelet activation (6). Therefore, platelet degranulation must be prevented during blood sampling and processing to measure true circulating TGF- β 1 levels (7). In addition, because even the best methods of plasma collection and processing can result occasionally in some platelet degranulation, the extent of platelet activation must be assessed in studies reporting TGF- β 1 plasma concentrations by determining plasma levels of platelet degranulation markers such as β -thromboglobulin or platelet factor 4 (7, 8).

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IN REPLY TO DR. BARTHELEMY-BRICHANT

To the Editor: In her letter, Dr Barthélemy correctly points out that the results of clinical studies investigating the relation between levels of transforming growth factor (TGF)- β and the risk of radiation pneumonitis (1–3) may be discrepant because of differences in the applied methodology. She raises the issue that measurements of TGF- β may be confounded by TGF- β released during platelet activation.

It is indeed true that platelets contain very high amounts of TGF- β and we were well aware of this when we started our trial. To avoid platelet degranulation during blood sampling and sample preparation, all our patients' blood samples were therefore collected (1) without the use of a tourniquet, (2) in EDTA tubes, and (3) the first tube was discarded. This protocol was based on previous experiments (4) in which we validated sample preparation as well as many other aspects (e.g., sensitivity and specificity) of the PAI-1 bioassay that was used in our clinical study (1). In these experiments, it was shown (4) that intentional platelet degranulation indeed lead to 5- to 17-fold higher values for plasma TGF- β values and resulted in large sample-to-sample variation. However, using the careful blood sampling described previously (and used in our clinical study), values from healthy human individuals determined with the PAI-1 assay