Collagen-water interaction for quantitative estimation of radiation-induced subcutaneous fibrosis by dielectric method

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Abstract: Radiation-induced subcutaneous fibrosis for six dose-fractionation schedules was evaluated with breast cancer patients by clinical scoring and dielectric measurements. Dielectric constant of the irradiated breast skin and contralateral untreated skin was measured at 300 MHz using an open-ended coaxial probe and a network analyzer. Using a Maxwell-Fricke mixture theory for particles in solution the collagen volume fraction of the dermis was calculated from the dielectric data. There was a statistically significant correlation ($p < 0.01$) between the collagen volume fraction and the incidence of subcutaneous fibrosis scored for the patients in the six dose-fractionation schedules. Dielectric measurement is a new tool for quantitative estimation of subcutaneous fibrosis.

INTRODUCTION

Subcutaneous fibrosis is a well defined late effect of the skin to radiotherapy. Several factors in the dermis and subcutis are suggested to be responsible for the development of this reaction although the injury of the cutaneous vessels is considered one of the most important [1].

Subcutaneous fibrosis has been scored clinically using different scales. Although there are only a few studies on the quantitation of radiation-induced fibrosis [2], more noninvasive, clinically applicable methods are needed.

The dielectric properties of many tissues have been widely investigated as a function of electromagnetic (EM) field frequency [3]. In the skin, the dielectric properties at high radiofrequencies are principally determined by tissue water content. The water content can be devided into free water and bound water related to proteins and proteoglycans. These macromolecules are covered by one or two layers of water molecules [4].

Since the subcutaneous fibrosis is related to the increasing amount of skin collagen and change in the ratio of various collagens [5], the skin late injury could be followed by dielectric measurements which reflect radiation-induced changes in tissue water deposition. Since collagen is the most numerous protein in the skin, the total proteins were approximated by the amount of collagen. In this study, collagen volume fraction calculated from dielectric parameters was compared with clinical incidence of subcutaneous fibrosis.

METHOD

Since subcutaneous fibrosis induces changes also in dermis [2], a two-layer skin model was developed to estimate the dielectric constant (ε) of the dermis [6]. The model eliminates the thickness variations of the skin between patients. To perform the correction, the thickness of the skin was measured with a 20 MHz ultrasound.

The dielectric constant (i.e. the real part of complex permittivity) of the skin was measured using an open-ended coaxial reflection method and a network analyzer [7]. An EM wave of 300 MHz was guided into the skin. The magnitude and the phase shift of the reflected waves were measured for the calculation of dielectric constant.

The dielectric constant of the irradiated and contralateral breast skin was measured for 35 breast cancer patients after postmastectomy radiotherapy with three techniques. Since each technique consisted of two beams, six dose-fractionation schelules of the skin were available (Table 1).

Table 1: Summary of six dose-fractionation scheludes and related incidence of subcutaneous fibrosis. Symbol "Ph 2" means a megavoltage photon beam with a dose of 2.0 Gy at build-up maximum. The symbols El and X describe the electron and superficial x-ray beams, respectively.

Treatment schelude	# of patients	Daily skin dose (Gy)	Total skin dose (Gy)	Incidence of sc. fibrosis
Ph 2	8	0.96	24.0	1/8
El 2	8	1.96	49.0	4/8
Ph 4	12	1.92	21.1	2/12
El 3.5	12	3.54	31.9	2/12
Ph 4	15	1.92	21.1	5/15
X 3.5	15	4.34	39.1	5/15

Collagen volume fraction p was calculated from the dielectric data using a Maxwell-Fricke mixture theory [3]:

$$\frac{\varepsilon_\infty - \varepsilon_w}{\varepsilon_\infty + \chi\varepsilon_w} = p\frac{\varepsilon_p - \varepsilon_w}{\varepsilon_p + \chi\varepsilon_w} , \qquad (1)$$

where ε_∞ is the high frequency dielectric constant (here 300 MHz), ε_w the dielectric constant of free water (=80),

ε_p the dielectric constant of protein (=5) and χ = 1.5 the shape factor for prolate particles. Since $\varepsilon_p << \varepsilon_w$, the resulting approximation for p can be expressed as

$$p \approx \frac{\chi(\varepsilon_w - \varepsilon_\infty)}{\varepsilon_\infty + \chi\varepsilon_w} = \frac{120 - 1.5\varepsilon_\infty}{120 + \varepsilon_\infty} \qquad (2)$$

RESULTS

Figure 1 illustrates the correlation between the collagen volume fraction calculated from the dielectric data and the incidence of subcutaneous fibrosis, when all grades (slight, moderate and severe) of fibrosis are included. The correlation was statistically significant also if only slight fibrosis was considered.

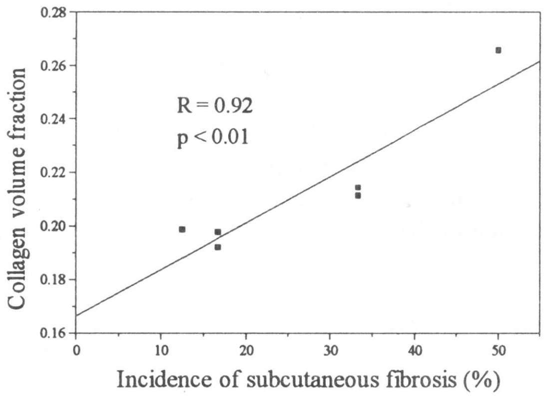

Figure 1. Collagen volume fraction vs. incidence of subcutaneous fibrosis.

DISCUSSION AND CONCLUSIONS

The correlation between the collagen volume fraction calculated from the dielectric data and the incidence of subcutaneous fibrosis suggests that the dielectric measurements might be useful, not only with the group of patients as in this study, but also as an individual basis for the follow-up of radiation reactions. Due to a small number of patients with moderate and severe fibrosis, we cannot conclude whether the method could differentiate between various grades of fibrosis. At present, the dielectric method is one of the most quantitative and tissue-specific techniques for the noninvasive estimation of subcutaneous fibrosis.

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