Reassessment of stopping power ratio uncertainties caused by mean excitation energies using a water-based formalism

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Purpose: In proton therapy planning, the accuracy of the Stopping Power Ratios (SPR) calculated in the stoichiometric CT calibration is affected by, among others, uncertainties on the mean excitation energies (I-values) of human tissues and water. Traditionally, the contribution of these uncertainties on the SPR has been conservatively estimated of the order of 1% or more for a reference tissue of known composition. This study provides a methodology that enables a finer estimation of this uncertainty, eventually showing that the traditional estimates of the uncertainty are too conservative.
Methods: Since human tissues contain water, a correlation exists between the I-values of tissues and water. As the SPR is the ratio of the tissue stopping power to that of water, this correlation decreases the uncertainty of the SPR. Our formalism considers this by expressing the I-value of the tissue as a function of the water weight fraction and the I-value of water, while applying Bragg's additivity rule only to the nonaqueous mixture of the tissue. For 22 reference tissue compositions, the SPR uncertainty was estimated by randomly sampling Gaussian distributions, based on ICRU data, for the I-values of water and the nonaqueous mixture, as well as for the water weight fraction.
Results: The relative standard deviation of the SPR, estimated at 150 MeV, is in the range of 0.1%–0.3% for soft tissues with an average water weight percentage of at least 60%. For tissues with a low water content (e.g., adipose and bones), this uncertainty is in the range of 0.5%–0.7%.
Conclusion: Uncertainties on the I-values of human tissues and water appear to have a significantly lower impact on the SPR uncertainty than traditionally expected. In the future, this may provide a rationale for using smaller distal and proximal margins on the target volume, provided that all other range uncertainty components are correctly estimated too. [https://doi.org/10.1002/mp.12949]

Key words: Bragg's additivity rule, human tissues, mean excitation energy, stopping power ratio, uncertainties

1. INTRODUCTION

In radiation therapy, the healthy tissues surrounding the tumor need to be spared as much as possible so as to reduce the side-effects of the treatment. One of the advantages of proton therapy over x-ray therapy is that protons have a finite range in matter, which enables drastic mitigation of the dose delivered to healthy tissues behind the tumor. The proton range is, however, quite sensitive to various sources of uncertainties,[1,2] which are approximately accounted for by adding a proximal and a distal margin to the target volume, or a performing a global density scaling of the CT image in robust optimizers. Although effective for ensuring the robustness of the treatment plan, these approaches increase the irradiated volumes and jeopardize the initial advantage of protons. A careful assessment of the range uncertainties is thus necessary.

The treatment plan is typically determined based on a Stopping Power Ratio (SPR) map, calculated from the patient's planning CT by using a scanner-specific stoichiometric calibration curve.[3] Establishing this calibration curve involves, among others, computing the SPRs of several reference human tissues, of which the compositions and densities are found in literature.[4,5] From these compositions and densities, we can derive all quantities necessary to compute stopping power ratios. Two quantities are primarily affected by the composition and the density: (a) the electronic density; (b) the mean excitation energy (the so-called "I-value"). The former can be measured by the CT through proper calibration. The second needs to be computed or derived from tables. In either case, uncertainties remain in the determination of the mean excitation energy, even if the atomic composition is perfectly known.

Paganetti[1] estimated the range uncertainty caused by I-value uncertainties to about 1.5% at 1 standard deviation. The underlying assumption was that the I-values of human tissues have relative standard deviations of 10%–15%. The influence of the correlation between the I-values of water and human tissues, however, was not considered in this study.

Yang et al.[2] adopted a different approach. They suggested that, due to the presence of water in tissues, a positive correlation exists between the I-values of human tissues and water, which makes the SPR uncertainty smaller than if the I-values were completely independent. This effect was observed in their numerical simulations because both the I-values of the tissue and water were computed with Bragg's elemental additivity rule and they considered 10% variations of all the elemental I-values simultaneously. They obtained average SPR uncertainties of 0.65%, 0.23% and 0.17% for bones, soft tissues and lung, respectively.

The aim of this work is to present an alternative formalism for calculating the I-value of a tissue, which explicitly expresses the abovementioned correlation. Unlike the method followed by Yang et al.,[2] this formalism allows simulating SPR uncertainties based on any I-value of liquid water independently of the elemental I-value of H and O used in the dry tissue. Thus, the latest ICRU recommendation of 78.0 eV can for instance be used, potentially providing a more accurate calculation of the tissue I-value than Bragg's elemental additivity rule.

2. METHODS

2.A. Background

The SPR of a tissue is generally calculated with the following formula[3]:

$$SPR = \rho_e^{rel} \frac{ln\left(\frac{2m_e c^2 \beta^2}{(1-\beta^2)e^{\beta^2}}\right) - lnI_t}{ln\left(\frac{2m_e c^2 \beta^2}{(1-\beta^2)e^{\beta^2}}\right) - lnI_w} \quad (1)$$

where ρ_e^{rel} is the relative electron density of the tissue (relative to water), I_t the mean excitation energy (I-value) of the tissue, I_w the I-value of liquid water, m_e the electron rest mass, c the velocity of light in vacuum, and β the proton velocity divided by c.

Due to a lack of I-value measurements for reference human tissues, these I-values are usually estimated using Bragg's elemental additivity rule[6,7]:

$$\ln(I_t) \approx \sum_i \frac{(\omega_i)_t \frac{Z_i}{A_i}}{\left(\frac{Z}{A}\right)_t} \ln I_i \quad (2)$$

where I_t is the I-value of the tissue, $(\omega_i)_t$ the mass fraction of element i in the tissue, I_i the I-value of element i, Z_i the atomic number of element i, A_i the atomic mass of element i, and $\left(\frac{Z}{A}\right)_t = \sum_i (\omega_i)_t \frac{Z_i}{A_i}$.

Using I-values of elemental substances with this additivity rule leads to errors due to the neglect of molecular binding and/or physical state effects (for gases vs condensed states).[6,7] Therefore, the ICRU reports 37 and 49 recommended a set of specific I-values for atomic constituents of compounds, with a distinction between gases and condensed states (Table 2.11 in ICRU report 49,[7] identical to Table 5.1 in ICRU report 37[6]). Although in theory an elemental I-value also depends on the type of compound, this simplified scheme allows estimating the I-values of a large number of compounds quite satisfactorily.[6,7]

2.A.1. *I-value of water*

During the commissioning of a proton therapy system, the beam energy is determined based on range measurements in a water phantom. An assumption is thus made regarding the I-value of liquid water for this energy calibration and, for consistency, the same I_w value must be used to compute SPR in the stoichiometric calibration of the CT scanner dedicated to treatment planning (see Eq. 1). Many different values, ranging from 67.2 eV up to 82.4 eV, have been proposed in literature for the I-value of liquid water (see, for example, the review in section 5.3 of ICRU Report 90[8]). Table I provides an historical overview of the I_w values recommended by the ICRU. The latest recommendation is 78.0 eV, but many treatment planning systems currently rely on the early recommendation of 75.0 eV.[2,9,10]

2.B. Water content-based formalism

In the conventional formalism, the I-value of a tissue is calculated by applying Bragg's additivity rule to the constituent atoms of the tissue (see Eq. 2). The ICRU Report 49 states, however, that "improved accuracy can be obtained by applying the additivity rule not to the constituent atoms, but to molecular fragments or functional groups".[1] Building further on this idea, the I-value calculation could be more accurate if, for instance, the water molecules of the tissue were treated separately so that an experimentally determined I-value of liquid water could be applied to them. For consistency, this value must be the same as the one appearing in the denominator of the SPR formula (Eq. 1), and the same as the reference value used during the commissioning of the proton therapy system. For the nonaqueous mixture of molecules

TABLE I. Historical overview of ICRU recommendations for the I-value of liquid water.[6–8,11,12]

Year	Source	Method	I-value (eV)
1984	ICRU Report 37	Measurements & calculations	75.0 ± 2.3
1993	ICRU Report 49	Same as in ICRU Report 37	
2005	ICRU Report 73	Calculation	67.2
2009	Errata and addenda for ICRU Report 73	Measurement	78.0 (tentative)
2016	ICRU Report 90	Measurements & calculations	78.0 ± 2.0

(the "dry tissue"), one can still use Bragg's additivity rule applied to the constituent atoms, for want of anything better.

To construct this alternative formalism, we start by expressing the elemental composition of the tissue as a function of the water weight fraction:

$$(\omega_i)_t = \frac{m_w(\omega_i)_w + m_{dt}(\omega_i)_{dt}}{m_t} = \omega_w(\omega_i)_w + (1-\omega_w)(\omega_i)_{dt} \quad (3)$$

where $(\omega_i)_t$ is the mass fraction of element i in the tissue, m_t the total mass of the tissue, m_w the mass of water in the tissue, m_{dt} the mass of "dry tissue" in the tissue, $(\omega_i)_w$ the mass fraction of element i in water, $(\omega_i)_{dt}$ the mass fraction of element i in the "dry tissue", and ω_w the water weight fraction of the tissue.

Inserting Eq. (3) into the conventional formalism (Eq. 2), gives us:

$$lnI_t \approx \frac{1}{\left(\frac{Z}{A}\right)_t}\left[\omega_w \sum_i (\omega_i)_w \frac{Z_i}{A_i} lnI_i + (1-\omega_w)\sum_i (\omega_i)_{dt}\frac{Z_i}{A_i} lnI_i\right] \quad (4)$$

which is also equivalent to:

$$lnI_t \approx \frac{1}{\left(\frac{Z}{A}\right)_t}\left[\omega_w \left(\frac{Z}{A}\right)_w lnI_{w,Bragg} + (1-\omega_w)\left(\frac{Z}{A}\right)_{dt} lnI_{dt}\right] \quad (5)$$

where

$$\left(\frac{Z}{A}\right)_w \equiv \sum_i (\omega_i)_w \frac{Z_i}{A_i}, \quad lnI_{w,Bragg} \equiv \frac{1}{\left(\frac{Z}{A}\right)_w}\sum_i (\omega_i)_w \frac{Z_i}{A_i} lnI_i, \quad (6)$$

$$\left(\frac{Z}{A}\right)_{dt} \equiv \sum_i (\omega_i)_{dt} \frac{Z_i}{A_i}, \quad lnI_{dt} \equiv \frac{1}{\left(\frac{Z}{A}\right)_{dt}}\sum_i (\omega_i)_{dt} \frac{Z_i}{A_i} lnI_i, \quad (7)$$

As such, the I-value of the tissue is expressed as a function of the I-value of liquid water ($I_{w,Bragg}$) and the I-value of the "dry tissue" (I_{dt}), both calculated through Bragg's additivity rule applied to their constituent atoms. To be consistent with the calibration of the proton therapy system, we choose to replace $I_{w,Bragg}$ in Eq. (5) by the reference I-value I_w used during the commissioning procedure. This brings us to the water content-based formalism adopted in this work:

$$lnI_t \approx \omega_w \frac{\left(\frac{Z}{A}\right)_w}{\left(\frac{Z}{A}\right)_t} lnI_w + (1-\omega_w)\frac{\left(\frac{Z}{A}\right)_{dt}}{\left(\frac{Z}{A}\right)_t} lnI_{dt}, \quad with \; lnI_{dt} \equiv \frac{1}{\left(\frac{Z}{A}\right)_{dt}}\sum_i (\omega_i)_{dt}\frac{Z_i}{A_i} lnI_i, \quad (8)$$

where the mass fraction of element i in the "dry tissue" is derived from Eq. (3):

$$(\omega_i)_{dt} = \frac{(\omega_i)_t - \omega_w(\omega_i)_w}{(1-\omega_w)}. \quad (9)$$

2.C. Comparison of different I-value and SPR calculation methods

The study was conducted for twenty-two reference tissues[4,5] of which the elemental composition and the water weight fraction are given in Table II. The SPRs of the tissues were calculated at 150 MeV, following four different approaches summarized in Table III. These will be called for the remaining of the paper the "nominal SPRs". The element I-values needed to compute these nominal SPRs were taken from ICRU 37 and 49. In the methods Bragg78 and Bragg75,

TABLE II. Water weight fractions ω_w and elemental mass compositions of the reference tissues.[4,5]

Reference tissue	ω_w	H	C	N	O	Na	Mg	P	S	Cl	K	Ca	Fe
Skeleton – cortical bone	0.122	3.4	15.5	4.2	43.5	0.1	0.2	10.3	0.3	0	0	22.5	0
Skeleton – yellow marrow	0.153	11.5	64.4	0.7	23.1	0.1	0	0	0.1	0.1	0	0	0
Adipose tissue 2	0.212	11.4	59.8	0.7	27.8	0.1	0	0	0.1	0.1	0	0	0
Skeleton – spongiosa	0.225	8.5	40.4	2.8	36.7	0.1	0.1	3.4	0.2	0.2	0.1	7.4	0.1
Breast (ICRU 44)	0.313	10.6	33.2	3.0	52.7	0.1	0	0.1	0.2	0.1	0	0	0
Skeleton – red marrow	0.397	10.5	41.4	3.4	43.9	0	0	0.1	0.2	0.2	0.2	0	0.1
Skin 1	0.586	10.0	25.0	4.6	59.4	0.2	0	0.1	0.3	0.3	0.1	0	0
Eye lens	0.641	9.6	19.5	5.7	64.6	0.1	0	0.1	0.3	0.1	0	0	0
Pancreas	0.733	10.6	16.9	2.2	69.4	0.2	0	0.2	0.1	0.2	0.2	0	0
Muscle – skeletal 2	0.741	10.2	14.3	3.4	71.0	0.1	0	0.2	0.3	0.1	0.4	0	0
Liver 2	0.745	10.2	13.9	3.0	71.6	0.2	0	0.3	0.3	0.2	0.3	0	0
Skeleton – cartilage	0.750	9.6	9.9	2.2	74.4	0.5	0	2.2	0.9	0.3	0	0	0
Heart 2	0.759	10.4	13.9	2.9	71.8	0.1	0	0.2	0.2	0.2	0.3	0	0
Kidney 2	0.766	10.3	13.2	3.0	72.4	0.2	0	0.2	0.2	0.2	0.2	0.1	0
Lung – inflated (ICRU 44)	0.78	10.3	10.5	3.1	74.9	0.2	0	0.2	0.3	0.3	0.2	0	0
Spleen	0.787	10.3	11.3	3.2	74.1	0.1	0	0.3	0.2	0.2	0.3	0	0
Blood – whole	0.790	10.2	11	3.3	74.5	0.1	0	0.1	0.2	0.3	0.2	0	0.1
GI tract – small intestine	0.806	10.6	11.5	2.2	75.1	0.1	0	0.1	0.1	0.2	0.1	0	0
Brain – gray matter	0.826	10.7	9.5	1.8	76.7	0.2	0	0.3	0.2	0.3	0.3	0	0
Testis	0.827	10.6	9.9	2	76.6	0.2	0	0.1	0.2	0.2	0.2	0	0
Ovary	0.828	10.5	9.3	2.4	76.8	0.2	0	0.2	0.2	0.2	0.2	0	0
Lymph (ICRU 44)	0.919	10.8	4.1	1.1	83.2	0.3	0	0	0.1	0.4	0	0	0

TABLE III. Overview of the different methods used to calculate the nominal SPR of the reference tissues.

Method	I_t calculation	Denominator of SPR formula
Bragg78	Bragg's elemental additivity rule (Eq. 2)	I_w = 78.0 eV
Bragg75	Bragg's elemental additivity rule (Eq. 2)	I_w = 75.0 eV
Water78	Water content-based formalism using I_w = 78.0 eV (Eq. 8)	I_w = 78.0 eV
Water75	Water content-based formalism using I_w = 75.0 eV (Eq. 8)	I_w = 75.0 eV

Depending on the method, the I-value of the tissue was calculated with either Bragg's elemental additivity rule or the water content-based formalism, whereas the I-value of water was set to either 78.0 eV or 75.0 eV.

I_t was calculated with Bragg's elemental additivity rule and different values of I_w were used in the denominator of the SPR formula. In present clinical practice, the most common approach is Bragg75, which uses I_w = 75.0 eV. Future facilities might, however, be inclined to adopt Bragg78 instead, to comply with the new ICRU recommendation for the I-value of liquid water (I_w = 78.0 eV). In methods Water78 and Water75, the water content-based formalism is used with I_w = 78.0 eV and I_w = 75.0 eV, respectively. In theory, the water content-based formalism provides a more accurate I_t calculation than Bragg's elemental additivity rule (see Section 2.A). The method Water78, which follows the latest ICRU recommendation for I_w, is therefore considered the most accurate method in this study.

2.D. Numerical simulations of SPR uncertainties

Evaluations of the SPR uncertainty caused by I-value uncertainties were carried out using each method from Table III. To estimate this uncertainty, variations of the SPR were simulated numerically through random sampling of Gaussian distributions for:

- I_t and I_w, when using methods Bragg78 and Bragg75,
- I_ω and I_{dt}, when using methods Water78 and Water75.

A relative standard deviation of 6% was assumed for I_t (in Bragg78 and Bragg75) and I_{dt} (in Water78 and Water75). It corresponds to an uncertainty of approximately 10% at the 90% confidence level. This choice was based on the ICRU guideline assigning an estimated uncertainty of 5%–10% at the 90% confidence level to the I-value of condensed compounds consisting predominantly of the elements H, C, N, O, F, or Cl (see Section 5 and footnote 10 in ICRU Report 37[6]). As for I_w, the standard deviations recommended by the ICRU[6,8] were used as well, namely 2.0 eV for I_w = 78.0 eV and 2.3 eV for I_w = 75.0 eV.

In a second stage, the sensitivity of the water content-based formalism to uncertainties on the water weight fraction was assessed by adding a Gaussian sampling for ω_w in the simulations Water78 and Water75. The assumed uncertainties were relatively large (see Table IV). For tissues with $(\omega_w)_{nominal} < 0.35$, the relative standard deviation of ω_w (σ_{ω_w}) was set to 15%. For tissues with a larger nominal water content, it was reduced to 0.6%–8.2%, to remain consistent with the upper limit $(\omega_w)_{max}$ imposed by the H and O contents of the tissue. In this case, $(\omega_w)_{max}$ was assumed to lie at 3 standard deviations from $(\omega_w)_{nominal}$.

3. RESULTS

3.A. Nominal I-values and SPRs at 150 MeV

Table V shows the nominal I-values of the reference tissues as calculated with Bragg's elemental additivity rule and the water content-based formalism using either I_w = 78.0 eV or I_w = 75.0 eV. Very similar results were obtained with Bragg's elemental additivity rule and the water content-based formalism using I_w = 75.0 eV, the results of the former being larger by 0.05%–0.4%. Somewhat larger differences were observed with the results of the water content-based formalism using I_w = 78.0 eV, Bragg's elemental additivity results being smaller than these by 0.5%–3.2%. In Table V, the tissues are ordered by increasing water weight fraction. As such, one can notice that the relative differences between the three I-value calculations increase as a function of the tissue water content.

For each of the calculation methods listed in Table III, the nominal SPR results at 150 MeV are compared in Table VI. In addition, Fig. 1 shows their relative differences with respect to the results of the water content-based formalism using I_w = 78.0 eV (method Bragg78). These relative differences are significantly smaller than those existing between the I_t values. At worst, they only reach up to ~0.4% in absolute value. Especially the methods involving either I_w = 75.0 eV lead to highly similar SPR results (see methods Bragg75 and Water75). These methods differ the most from the reference method (Water78) for tissues of low water content. The opposite tendency is, however, observed for method Bragg78, in which I_t is calculated with Bragg's elemental additivity rule and I_w is set to 78.0 eV in the denominator of the SPR formula.

3.B. Simulations of the SPR uncertainties at 150 MeV

To estimate the SPR uncertainties caused by I-value uncertainties, SPR distributions were sampled numerically as described in Section 2.B. Slightly skewed bell-shaped distributions, such as those shown in Fig. 2, were obtained for all simulations. It turned out that the median of the distributions laid very close to the mean and coincided largely with the nominal SPR (within 0.002%). This was also observed when using the other SPR calculation methods. In general, the small asymmetry of the distributions made it rather meaningless to report asymmetric SPR uncertainties. The standard deviation was thus used

TABLE IV. Mean and relative standard deviation assumed for the water weight fraction ω_w of reference tissues.

Reference tissue	Mean ω_w	Relative standard deviation of ω_w (σ_{ω_w})
Skeleton – cortical bone	0.122	15%
Skeleton – yellow marrow	0.153	15%
Adipose tissue 2	0.212	15%
Skeleton – spongiosa	0.225	15%
Breast (ICRU 44)	0.313	15%
Skeleton – red marrow	0.397	8.2%
Skin 1	0.586	4.7%
Eye lens	0.641	4.5%
Pancreas	0.733	2.2%
Muscle – skeletal 2	0.741	2.6%
Liver 2	0.745	2.7%
Skeleton – cartilage	0.750	3.9%
Heart 2	0.759	2.2%
Kidney 2	0.766	2.1%
Lung – inflated (ICRU 44)	0.78	2.7%
Spleen	0.787	2.0%
Blood – whole	0.790	2.1%
GI tract – small intestine	0.806	1.6%
Brain – gray matter	0.826	1.5%
Testis	0.827	1.4%
Ovary	0.828	1.5%
Lymph (ICRU 44)	0.919	0.6%

TABLE V. Nominal I-values of the reference tissues, calculated *via* three different methods: Bragg's elemental additivity rule (Bragg78 and Bragg75), the water content-based formalism using I_w = 78.0 eV (Water78), and the water content-based formalism using I_w = 75.0 eV (Water75).

	I_t (eV)		
Reference tissue	Bragg78 and Bragg75	Water78	Water75
Skeleton – cortical bone	111.97	112.49	111.91
Skeleton – yellow marrow	63.90	64.24	63.86
Adipose tissue 2	64.78	65.26	64.72
Skeleton – spongiosa	78.40	79.04	78.33
Breast	70.29	71.07	70.20
Skeleton – red marrow	69.17	70.15	69.06
Skin 1	72.81	74.33	72.63
Eye lens	74.29	75.99	74.08
Pancreas	73.42	75.34	73.20
Muscle – skeletal 2	74.62	76.60	74.38
Liver 2	74.82	76.81	74.58
Skeleton – cartilage	78.02	80.13	77.77
Heart 2	74.31	76.33	74.07
Kidney 2	74.66	76.70	74.41
Lung (inflated)	75.17	77.26	74.91
Spleen	74.98	77.09	74.73
Blood – whole	75.20	77.33	74.95
GI tract – small intestine	74.28	76.42	74.03
Brain – gray matter	74.79	76.99	74.52
Testis	74.73	76.93	74.46
Ovary	75.01	77.23	74.75
Lymph	75.45	77.93	75.16

as the estimator for the SPR uncertainty. Statistical characteristics of the distributions are given in Table VII for Water78.

For the methods using the water content-based formalism (Water78 and Water75), the sensitivity of the simulations to uncertainties of the water weight fraction ω_w was also investigated. The results are also shown in Table VII using the ω_w uncertainties (σ_{ω_w}) from Table IV. The comparison shows that including these ω_w uncertainties had no significant impact on the relative standard deviations of the SPR distributions. The same was observed for Water75 as well. Depending on the SPR calculation method used in the simulations, different relative standard deviations were obtained. Figures 3 and 4 compare the results of two simulations based on the same nominal I_w value (78.0 eV and 75.0 eV, respectively) but using different I_t calculation methods: either Bragg's elemental additivity rule or the water content-based formalism. The results in these two figures are very similar. In both cases, the simulations using the water content-based formalism yielded smaller estimated SPR uncertainties than those using Bragg's elemental additivity rule for I_t. With the water content-based formalism, the results also depend on the water content of the tissue: the larger the water weight fraction, the smaller the SPR uncertainty. In the simulations using Bragg's elemental additivity rule, however, this trend was not observed.

Quantitatively speaking, all simulations predicted relative SPR uncertainties lower than 1%. With the water content-based formalism (Water78 and Water75), the predicted uncertainties varied between ~0.1% and 0.7%–0.8%, depending on the water content of the tissue. With Bragg's elemental additivity rule (Bragg75 and Bragg78), uncertainties of 0.8%–0.9% were obtained for all tissues.

4. DISCUSSION

Relative differences between the nominal I_t values obtained through Bragg's elemental additivity rule and those computed with the water content-based formalism using I_w = 78.0 eV or I_w = 75.0 eV reach up to 3.2% and 0.4%, respectively. The reason hereof is that Bragg's elemental additivity rule is equivalent to the water content-based formalism with $I_w = I_{w,Bragg}$= 75.3 eV (this value being 3.5% smaller than 78.0 eV and 0.4% larger than 75.0 eV). Given the role of ω_w in Eq. (8), the larger the water content of the tissue, the more the I_w differences affect the calculation of I_t.

Relative differences in the SPRs resulting from I_t differences are, in comparison to these, much smaller (see Table VI and Fig. 1). For tissues of low water content, the I_t differences are so small that the SPR calculation is essentially sensitive to the differences in the denominator of the SPR formula (I_w). For tissues of high water content, however, the SPR calculation is mostly sensitive to the degree of

TABLE VI. Nominal SPR of the reference tissues at 150 MeV, calculated following four different methods Bragg's elemental additivity rule using I_w = 78.0 eV and 75.0 eV (Bragg78 and Bragg75, respectively), and the water content-based formalism using I_w = 78.0 eV and I_w = 75.0 eV (Water78 and Water75, respectively).

Method	Bragg78	Bragg75	Water78	Water75
Skeleton – cortical bone	1.7017	1.6936	1.7007	1.6937
Skeleton – yellow marrow	1.0061	1.0013	1.0055	1.0014
Adipose tissue 2	0.9729	0.9683	0.9720	0.9684
Skeleton – spongiosa	1.1492	1.1437	1.1481	1.1438
Breast	1.0272	1.0223	1.0258	1.0225
Skeleton – red marrow	1.0382	1.0332	1.0364	1.0334
Skin 1	1.0871	1.0819	1.0844	1.0822
Eye lens	1.0609	1.0558	1.0580	1.0562
Pancreas	1.0418	1.0368	1.0385	1.0372
Muscle – skeletal 2	1.0461	1.0411	1.0427	1.0415
Liver 2	1.0556	1.0505	1.0522	1.0510
Skeleton – cartilage	1.0833	1.0782	1.0798	1.0786
Heart 2	1.0485	1.0434	1.0450	1.0438
Kidney 2	1.0469	1.0419	1.0435	1.0423
Lung (inflated)	0.259	0.2578	0.2581	0.2579
Spleen	1.0563	1.0513	1.0528	1.0517
Blood – whole	1.055	1.0499	1.0514	1.0504
GI tract – small intestine	1.0305	1.0255	1.0269	1.0260
Brain – gray matter	1.0404	1.0354	1.0367	1.0358
Testis	1.0397	1.0347	1.0360	1.0351
Ovary	1.0482	1.0432	1.0445	1.0436
Lymph	1.0303	1.0254	1.0263	1.0259

consistency between I_w in the denominator and the I-value directly or indirectly used for water in the I_t calculation. The water content-based formalism is perfectly consistent in this regard and, therefore, methods Water78 and Water75 yield very similar results for tissues of high water content. Similar results are also obtained with method Bragg75, which has a relatively high degree of consistency since I_w in the denominator equals 75.0 eV and the I-value indirectly used for water in the I_t calculation is $I_{w,Bragg}$= 75.3 eV.

Four different approaches to simulate SPR uncertainties caused by I-value uncertainties have been compared in the Figs. 3 and 4. Unlike methods based on Bragg's elemental additivity rule (Bragg78 and Bragg75), methods using the water content-based formalism (Water78 and Water75) allow taking the correlation between I_t and I_w into account. In Bragg78 and Bragg75, the sampling of I_t is indeed independent from the sampling of I_w. In Water78 and Water75, however, the sampled value of I_w is systematically reused in the sampling of I_t, in which only the I-value of the dry tissue is sampled independently. As shown in the Figs. 3 and 4, the correlation between I_t and I_w leads to a reduction in the relative standard deviation of the SPR distribution compared to simulations based on methods Bragg78 and Bragg75. Indeed, any difference between the sampled and the nominal value of I_w in the SPR denominator gets compensated, to some extent, by the same difference occurring for I_w in the SPR numerator. The larger the water content of the tissue, the larger this compensation. Therefore, the relative standard deviation of the SPR decreases as a function of the water weight fraction. This compensating effect being absent in Bragg78 and Bragg75, such simulations lead to overestimated relative standard deviations, which are independent of the water weight fraction. Methods Bragg78 and Bragg75 are thus ill adapted for simulating SPR uncertainties caused by I-value uncertainties.

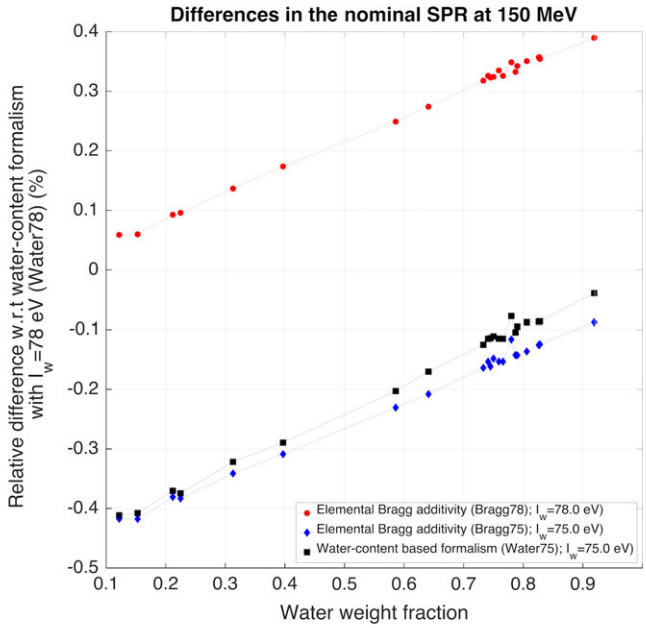

FIG. 1. Comparison of the nominal SPR at 150 MeV obtained through different calculation methods, as a function of water weight fractions of the reference tissues. The graph shows the relative differences with respect to the results obtained with Water78,. The red dots and blue diamonds represent the results of the methods based on Bragg's elemental additivity rule for I_t, with I_w = 78 eV (Bragg78) and I_w = 75 eV (Bragg75) in the SPR denominator, respectively. The black squares represent the results of the water content-based formalism with I_w = 75 eV (Water75). [Color figure can be viewed at wileyonlinelibrary.com]

Even though Water78 and Water75 were based on different mean values of I_w, they resulted in nearly the same relative standard deviations of the SPR, because the relative standard deviations of I_w were quite close in both simulations (2.6% and 3.1%, respectively).

The robustness of the water content-based formalism to uncertainties on the water weight fraction appeared to be excellent (see Table VII). As a matter of fact, Eq. (8) is equivalent to:

$$lnI_t \approx lnI_{t,Bragg} + \omega_w \frac{\left(\frac{Z}{A}\right)_w}{\left(\frac{Z}{A}\right)_t} \left[lnI_w - \; lnI_{w,Bragg}\right] , \qquad (10)$$

where $I_{t,Bragg}$ is the I-value of the tissue calculated following Bragg's elemental additivity rule. Since I_w and $I_{w,Bragg}$ take quite similar values, the term containing the water weight fraction ω_w is pretty small compared to $lnI_{t,Bragg}$. For this reason, the I_t calculation is not highly sensitive to ω_w uncertainties.

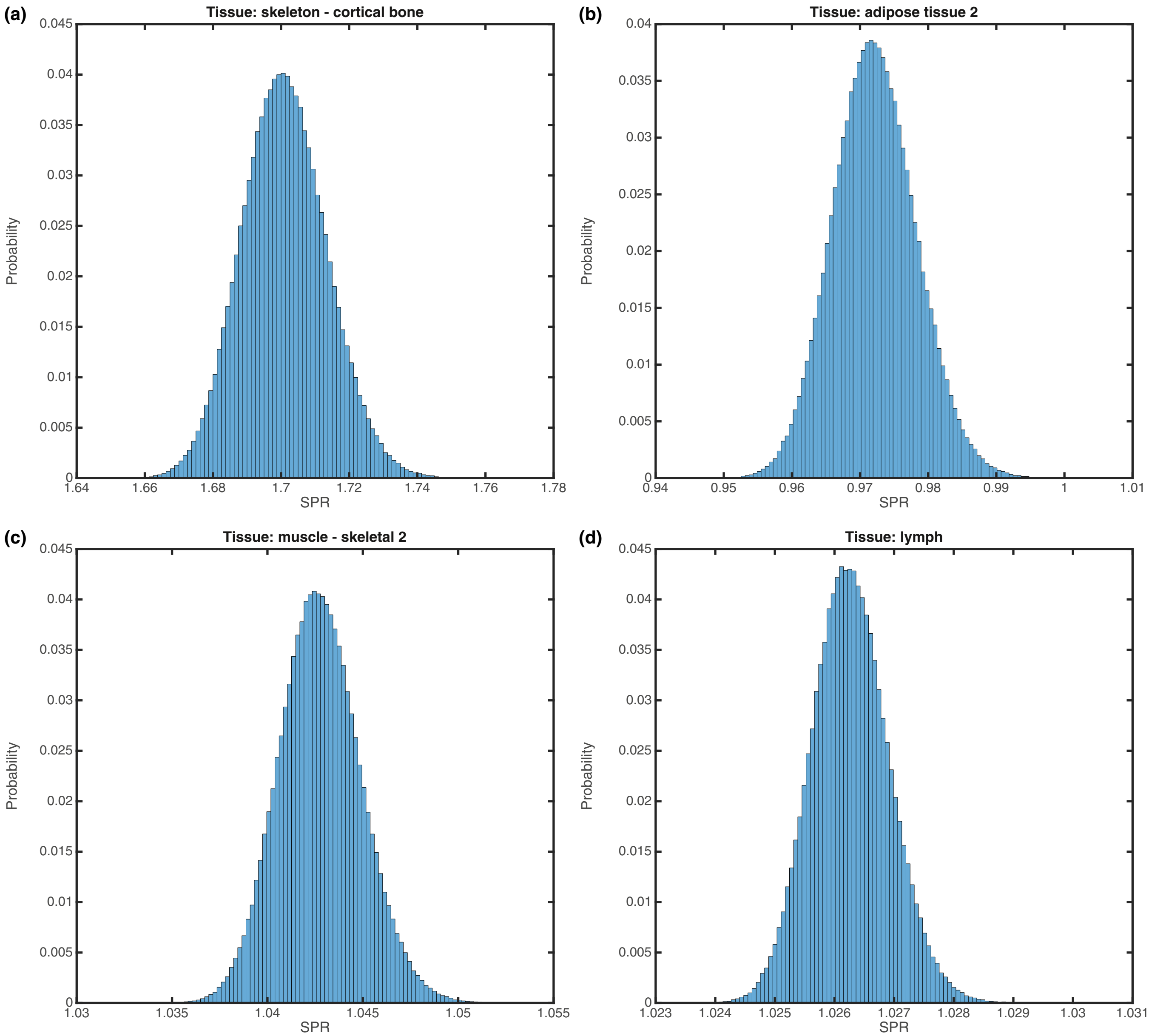

FIG. 2. SPR distribution due to uncertainties in the I-values and the water weight fraction for (a) skeleton – cortical bone, (b) adipose tissue 2, (c) muscle – skeletal 2, and (d) lymph, simulated at 150 MeV with the water content-based formalism using 78.0 eV for the I-value of water (Water78). [Color figure can be viewed at wileyonlinelibrary.com]

The nominal value of Water78 has been taken as the reference value in this study. As far as the nominal SPR values of methods Bragg78, Bragg75, and Water75, are concerned, their relative bias with respect to the reference Water78 are compared to the simulated SPR uncertainties (of reference) in Fig. 5. The nominal SPRs calculated with Bragg75 and Water75 mostly lie within 1.5 standard deviations from the reference SPR (the factor 1.5 has been chosen to be consistent with Paganetti's table[1]). The same is true with Bragg78, but only for tissues of relatively low water content ($\omega_w < 0.65$). For tissues of higher water content, the probability of having errors in the nominal SPRs appears to be much larger with Bragg78 than with Bragg75, because the latter involves a greater degree of consistency regarding the I-value of water (see Section 4.A). This is again due to the close proximity between the value of I_w used in the numerator and the denominator in Bragg75 ($I_{w,Bragg}$= 75.3 eV). Because most tissues lie in the high water-content region, our results suggest that consistency is the most important aspect for reducing the SPR uncertainty. The inconsistent usage of I_w in the numerator and in the denominator, even using a more accurate value for I_w, will improve accuracy only for a few tissues like bone or adipose and worsen it otherwise. At the 1.5 standard deviation level and considering Water78 and Water75, uncertainties are below 0.5% for a water weight fraction superior to 0.6. The choice of I_w would only marginally change the

TABLE VII. Statistical characteristics of the SPR distributions due to I-value uncertainties, simulated at 150 MeV with the water content-based formalism using 78.0 eV for the I-value of water (Water78), with the uncertainty σ_{ω_w} on the water content equaling zero or as defined in Table IV.

Reference tissue	Mean SPR (with $\sigma_{\omega_w} = 0$ and σ_{ω_w} as in Table IV)	Relative standard deviation ($\sigma_{\omega_w} = 0$)	Relative standard deviation (σ_{ω_w} as in Table IV)	Percent deviation of the median SPR w.r.t. the mean SPR ($\sigma_{\omega_w} = 0$)	Percent deviation of the median SPR w.r.t. the mean SPR (σ_{ω_w} as in Table IV)
Skeleton – cortical bone	1.700	0.7%	0.7%	−0.018%	−0.019%
Skeleton – yellow marrow	1.006	0.7%	0.7%	−0.016%	−0.017%
Adipose tissue 2	0.972	0.6%	0.6%	−0.015%	−0.017%
Skeleton – spongiosa	1.148	0.6%	0.6%	−0.016%	−0.015%
Breast	1.026	0.6%	0.6%	−0.013%	−0.015%
Skeleton – red marrow	1.037	0.5%	0.5%	−0.013%	−0.012%
Skin 1	1.084	0.3%	0.3%	−0.008%	−0.009%
Eye lens	1.058	0.3%	0.3%	−0.007%	−0.008%
Pancreas	1.039	0.2%	0.2%	−0.005%	−0.005%
Muscle – skeletal 2	1.043	0.2%	0.2%	−0.005%	−0.006%
Liver 2	1.052	0.2%	0.2%	−0.005%	−0.006%
Skeleton – cartilage	1.080	0.2%	0.2%	−0.005%	−0.006%
Heart 2	1.045	0.2%	0.2%	−0.004%	−0.005%
Kidney 2	1.044	0.2%	0.2%	−0.004%	−0.005%
Lung (inflated)	0.2582	0.2%	0.2%	−0.004%	−0.005%
Spleen	1.053	0.2%	0.2%	−0.004%	−0.004%
Blood – whole	1.051	0.2%	0.2%	−0.004%	−0.004%
GI tract – small intestine	1.027	0.2%	0.2%	−0.004%	−0.004%
Brain – gray matter	1.037	0.1%	0.1%	−0.003%	−0.004%
Testis	1.036	0.1%	0.1%	−0.003%	−0.004%
Ovary	1.045	0.1%	0.1%	−0.003%	−0.004%
Lymph	1.0263	0.1%	0.1%	−0.001%	−0.002%

picture for Water78 and Water75 methods, since the uncertainties (standard deviations) are overall unaffected by the change in I_w (see Figs. 3 and 5), and since the nominal SPR varies by less than 0.5%.

It is important to mention that we have ignored the uncertainty on the atomic composition. The uncertainties provided in Table 5.5 of ICRU report 37 are consistent with this approach (the uncertainty provided is flat for similar tissues). The estimation of the impact of I-values uncertainties previously reported in literature[1] also follows this assumption,[13] which enables to add the effect on the stopping power ratio can in quadrature. This results trivially from the independency of the uncertainty on the I-value on the composition.

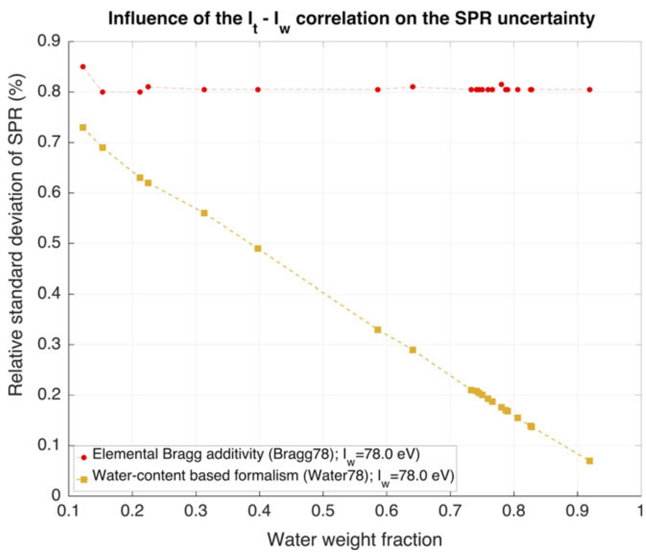

FIG. 3. Relative standard deviation of the SPR simulated at 150 MeV, as a function of the water weight fractions of the reference tissues. Simulations based on an I-value of (78.0 ± 2.0) eV for water. The red circles correspond to the results based on Bragg's elemental additivity rule (Bragg78), the yellow squares to those based on the water content-based formalism (Water78). [Color figure can be viewed at wileyonlinelibrary.com]

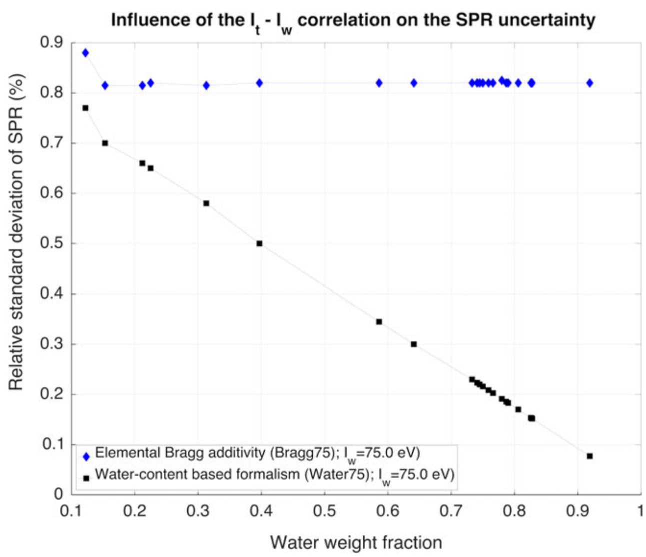

FIG. 4. Relative standard deviation of the SPR simulated at 150 MeV, as a function of the water weight fractions of the reference tissues. Simulations based on an I-value of (75.0 ± 2.3) eV for water. The blue diamondscirc correspond to the results based on Bragg's elemental additivity rule (Bragg75), the black squares to those based on the water content-based formalism (Water75). [Color figure can be viewed at wileyonlinelibrary.com]

Our approach consists in applying a "first order correction" to the Bragg additivity rule by applying the additivity rule to the water molecules instead of the constituent atoms in order to take into account the effect of chemical bonds, as suggested by Sabin et al[13] or Besemer et al.[14] A second-order correction would be to additionally take into account the effect of the interaction of water molecules with the surrounding. Our interpretation of the results relies on the

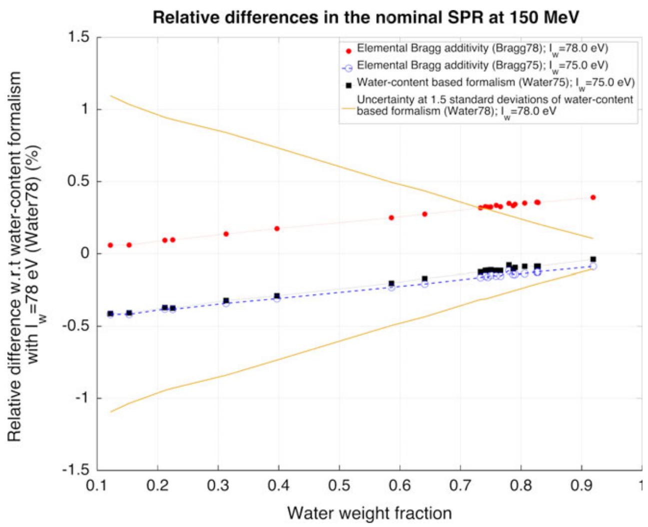

FIG. 5. Relative differences in the methods Bragg78 (red solid circle), Bragg75 (blue open circle) and Water75 (black square) with respect to the water content-based formalism with I_w = 78 eV (Water78), for the nominal SPR at 150 MeV, as a function of the water weight fraction. These relative differences are compared to the relative SPR uncertainty (due to contribution of elements I-value uncertainty only), also simulated with Water78 (solid line (gold)). [Color figure can be viewed at wileyonlinelibrary.com]

assumption that we can neglect this second order correction, that is, assuming water alone behaves the same way as water in a tissue from the I-value standpoint. Although ICRU report 37 indicates that such assumption should be safe, an experimental verification of this assumption would definitely strengthen our conclusions. Experimental data are under acquisition by our research group and will be disclosed in future publications. However, data on experimental verifications of SPR predictions with DECT have been recently reported.[15–17] In all three studies, animal tissue samples were used. The results seem consistent with our hypothesis that range uncertainties due to uncertain I-values are negligible in tissues with high water content.

The formalism developed in this study and the results focuses on the estimation of the uncertainties in the determination of the SPR for biological tissues due to uncertainties on the I-value. However, a few recommendations may also be suggested for the calibration of treatment planning systems, especially when they rely at some point on reference biological tissues for their calibration (e.g., the stoichiometric method,[3] its extension to DECT,[18] . . .). In such case, our methodology can be used as such to compute the reference SPRs, provided that a rough estimation of the water content is available. In any case, the most important is to ensure the consistency of the I_w selected for the computation of the stopping power in the numerator and the denominator. Inconsistency is the biggest source of uncertainty for materials with a high water content, which is the case of most tissues in the human body. In case of doubt, our results suggest that it is preferable to compute the SPR using a consistent and thorough application of the Bragg additivity rule at the atomical level everywhere in the formula leading to the SPR.

5. CONCLUSIONS

A water content-based formalism for calculating I-values of human tissues has been presented. It explicitly expresses the correlation existing between the I-values of human tissues and water. When using the latest ICRU recommendation for the I-value of liquid water, this formalism potentially provides tissue I-values less sensitive to uncertainty on elements I-values than Bragg's elemental additivity rule.

For reference tissues of known elemental compositions, SPR uncertainties caused by I-value uncertainties were simulated using the water content-based formalism, while following the ICRU guidelines on the Bragg additivity uncertainty for the I-value of the dry tissue (~6%). The uncertainties on the SPR were found to decrease as a function of the water weight fraction of the tissue. At 150 MeV, the obtained relative standard deviations of the SPR were of 0.1%–0.3% for soft tissues with an average water weight percentage of at least 60%, and of 0.5%–0.7% for fatty and bony tissues. The robustness of the water content-based formalism to uncertainties on the water weight fraction was shown to be excellent.

Our study suggests, therefore, that uncertainties in the I-values of human tissues and water have a significantly lower impact on the SPR uncertainty than initially expected. In the future, this may provide a rationale for using smaller margins on the target volume, provided that all other range uncertainty components are correctly estimated too.

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CONFLICTS OF INTEREST

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