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Estimate of the impact of FDG-avidity on the dose required for head and neck radiotherapy local control

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Abstract

Background and purpose—Although FDG-avid tumors are recognized as a potential target for dose escalation, there is no clear basis for selecting a boost dose to counter this apparent radioresistance. Using a novel analysis method, based on the new concept of an outcome-equivalent dose, we estimate the extra dose required to equalize local control between FDG-avid and non-avid head and neck tumors.

Materials and methods—Based on a literature review, five reports of head and neck cancer (423 patients in total), along with an internal validation dataset from our institution (135 oropharynx patients), were used in this analysis. To compensate for the heterogeneity among multi-institutional patient cohorts and corresponding treatment techniques, local control data of the cohorts were fit to a single dose–response curve with a clinically representative steepness (γ_{50} = 2), thereby defining an 'outcome-equivalent dose' (OED) for each institutional cohort. Separate dose–response curves were then determined for the FDG-avid and FDG-non-avid patient cohorts, and the ratio of TD_{50} (tumor dose required for 50% of control) values between the high- and low-FDG-uptake groups ($TD_{50,high}/TD_{50,low}$) was estimated, resulting in an estimated metabolic dose-modifying factor (mDMF) due to FDG-avidity.

Results—For individual datasets, the estimated mDMFs were found to be in the range of 1.07–1.62, decreasing if the assumed slope (γ_{50}) increased. Weighted logistic regression for the six datasets resulted in a mDMF of 1.19 [95% CI: 1.04–1.34] for a γ_{50} value of 2, which translates to a needed dose increase of about 1.5 Gy per unit increase in the maximum standardized uptake value (SUV_m) of FDG-PET [95% CI: 0.3–2.7]. Assumptions of lower or higher γ_{50} values (1.5 or 2.5) resulted in slightly different mDMFs: 1.26 or 1.15, respectively. A validation analysis with seven additional datasets, based on relaxed criteria, was consistent with the estimated mDMF.

Conclusions—We introduced a novel outcome-equivalent dose analysis method to estimate the dose– response modifying effect of FDG uptake variation. To reach equal response rates, FDG-

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Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.03.018.

avid tumors are likely to require 10% to 30% more dose than FDG-non-avid tumors. These estimates provide a rational starting point for selecting IMRT boosts for FDG-avid tumors. However, independent tests and refinements of the estimated dose-modifying effect, using high-quality prospective clinical trial data, are needed.

Keywords

FDG-PET; Head and neck tumor; Boost dose; Local control; Meta-analysis; Inter-institutional heterogeneity

Many common tumors exhibit an increased glucose uptake as a result of upregulated glycolysis [1], which can be detected via fluorodeoxyglucose positron emission tomography (FDG-PET, or simply FDG). FDG-PET has become an important diagnostic tool for cancer detection, staging, and target definition [2,3], as well as for monitoring tumor response after treatment [4,5].

Although there are some contrary results [6,7], many clinical studies have shown that the uptake of FDG, usually measured as the maximum standardized uptake value (SUV_m), is a significant predictor of prognosis for many tumor sites, including head and neck cancer [8–10]. Moreover, high FDG uptake is correlated with increased local failure and shorter survival [11–13]. The precise mechanism causing tumors with larger SUVs to exhibit a poorer treatment response is unknown. Tumors with a high SUV may: (i) consist of a higher tumor cell density or greater tumor/stroma cell ratio [14], (ii) be more metabolically active and consequently exhibit a higher proliferation rate, (iii) be more hypoxic [15,16], (iv) exhibit a higher DNA repair capacity [17], or some combination of these.

Due to careful studies registering regions of local failure with pre-treatment scans, there is some evidence that the region of highest FDG uptake might also be the region of highest radioresistance for head and neck cancer [18,19] and lung cancer [20,21]. This argues for the existence of tumor sub-regions corresponding to areas of high FDG uptake, that are radioresistant, in contrast to a shared phenotype of a particularly radioresistant tumor.

Based on clinical outcomes, the FDG-avid region in a tumor is recognized as a possible target for dose escalation. Several planning and optimization studies have assessed the feasibility of dose boosting on a sub-volume of a tumor, based on a FDG-PET image, using intensity modulated radiation therapy (IMRT) [22,23]. A key missing factor in the research on dose boosting, however, is a useful estimate of the quantity of extra dose required to compensate for FDG-avidity, compared with the population average or FDG-non-avid tumors. In this work, we estimated the metabolic dose-modifying factor (mDMF) due to FDG-avidity from clinical outcome data, based on the ratio of TD_{50} (tumor dose required for 50% of control) values between FDG-avid and FDG-non-avid tumors.

In order to estimate the extra dose required to compensate for increased FDG-avidity, we introduce a novel analysis method, we call the ‘outcome-equivalent dose’ (OED) method. The method accounts for the inevitable variability among radiotherapy patient cohorts regarding patient, disease, and treatment factors. Without accounting for these variations in local control rates, even for nominally similar treatment doses, the impact of FDG-avidity

would be assumed to be constant. This is clearly not the case comparing cohorts with overall high local control rates, where the impact of FDG variations is small, vs. a cohort with local control rate near 50%, where the impact of FDG variation is maximized. This analysis method is general, and therefore can be applied to estimate the impact of other risk factors known to affect dose response in heterogeneous cohorts, by partially compensating for the effects of other confounding factors.

Materials and methods

Inclusion criteria

A literature review was performed for reports of outcome comparisons between FDG-avid and FDG-non-avid cohorts diagnosed with head and neck squamous cell carcinoma (HNSCC) and treated with radiation therapy (RT). Initially, nearly 40 relevant studies were identified (see Supplementary materials). We included studies in which cohorts were determined based on the maximum standardized uptake values (SUV_m) of FDG-PET and the prescribed dose to the primary tumor and the resulting local control rate were reported. We further restricted our analysis to studies that used the median SUV_m value as the cut-off, instead of the statistically 'best' cut-off value, in order to maximize consistency and reduce consequent overestimation of effect. To date, SUV_m quantification is not completely consistent between institutions [24], which adds to some variability between reports. A limitation of our study is that the effect of chemotherapy, which most definitive RT patients receive, was not evaluable and therefore, ignored. However, clinical dataset variability including treatment techniques, fractionation schemes, doses, HPV status, and chemotherapy regimens, etc., was implicitly dealt with using the 'outcome-equivalent dose' method.

Clinical datasets included

Out of the reviewed studies, 5 studies satisfied the inclusion criteria: (i) patient cohorts with HNSCC; (ii) definitive RT with reported prescribed dose to primary tumor; and (iii) local control rates for high- and low-FDG-uptake groups separated by median SUV_m [25–29]. Eligibility tests for all reviewed studies are shown in Supplementary Table 1.

MSKCC internal validation dataset

In order to test the consistency of this analysis with our institutional data, we included an internal validation dataset. All MSKCC oropharynx cancer patients who were treated with definitive IMRT with conventional fractionation in the years 2004 to 2008 were considered for inclusion [30]. Among a total of 176 such oropharynx patients with pre-treatment FDG-PET images, 41 patients were excluded from this analysis: 39 patients who received surgery, 1 patient who died during treatment, and 1 patient whose SUV_m value was not reported. Hence, 135 patients were included in this analysis, as shown in Table 1.

The median SUV_m value for primary tumors was 13.9 [(kBq/ml)/(kBq/g)],[1] and patients were separated into two groups based on the median SUV_m. Except for T-stage ($p = 0.026$), all other patient characteristics were not statistically different between these two groups.

[1]The SUV_m values become dimensionless under the assumption that the tissue density is 1 g/ml.

Most patients with a T1 stage fell into the lower SUV_m group, while more patients with T2 and T4 stages were classified into the high SUV_m group. Correspondingly, when T-stage was separated into two groups (T1/2 vs. T3/4), the statistical difference between high- and low-FDG groups disappeared ($p = 0.441$). The median primary tumor dose was 70 Gy and the median treatment duration was 45 days. Except for 3 patients, all patients received concurrent chemotherapy. The high rate of local control has been reported elsewhere but may be related to HPV status [31].

From the 5 published datasets and our internal dataset, a total of 558 patients were thus included in this analysis; they are summarized in Table 2.

Logistic TCP model

A logistic tumor control probability (TCP) model was used to derive dose response curves from clinical outcome data. In the modified-logistic TCP model, the dose–response relation can be determined by the following equation [32]:

$$\mathrm{TCP}=\frac{1}{1+\left(\frac{\mathrm{TD}_{50}}{D}\right)^{4\gamma_{50}}} \quad (1)$$

where TCP is tumor control probability as a function of dose (D), TD_{50} is the tumor dose required to achieve a 50% rate of control, and γ_{50} is the normalized slope of the TCP curve at TD_{50}. The logistic TCP model was applied in the estimation of the outcome-equivalent dose, the TD_{50} ratio for individual clinical data, and logistic regression for whole datasets.

The clinically relevant slope of the dose response curve (γ_{50}) for human tumors has been explored for similar patient cohorts with different dose levels. Based on reviews of those studies, the most likely γ_{50} value for head and neck tumors was assessed to be about 2, with a range of 1.5–2.5 [33–36].

Outcome-equivalent dose

This analysis dealt with the clinical outcomes of heterogeneous patient cohorts treated at different institutions with different techniques. Therefore, direct comparison of the outcomes based only on the nominal radiation dose was not feasible. As shown in Table 1, the local control rates for different trials are significantly different, although the prescribed doses were similar.

Other than radiation dose, many other factors might affect treatment outcome. These include: tumor-specific factors, such as primary tumor site, size, and stage; patient-specific factors, such as race, age, and gender; and institution-specific factors, such as RT technique, fractionation scheme, and chemotherapy. However, it is impractical to evaluate the individual effect of these factors separately.

To incorporate the effects from these factors into the analysis, we determined an outcome-equivalent dose, instead of using the nominal dose (Fig. 1). The equivalent dose was derived from the total local control rate (before separating the high- vs. low-FDG-uptake groups) of each dataset. The equivalent dose was estimated from a logistic dose response curve, which

was derived from the average TD_{50} value of the total datasets for a typical γ_{50} value known for HNSCC. The total local control rate of each dataset was projected onto the dose response curve, and the equivalent dose was derived for each trial.

Estimation of mDMF due to FDG-avidity

The mDMF of FDG-avidity was estimated from the ratio of TD_{50} values between FDG-avid and FDG-non-avid tumors, split by the median SUV_m values. With a known γ_{50} value, the TD_{50} value can be calculated directly from TCP data, based on Eq. (1). For an individual trial, the mDMF was simply estimated from the following equation:

$$\mathrm{mDMF}=\frac{\mathrm{TD}_{50,\mathrm{high}}}{\mathrm{TD}_{50,\mathrm{low}}}=\frac{D_{\mathrm{high}}\left(\frac{1}{\mathrm{TCP}_{\mathrm{high}}}-1\right)^{1/4\gamma_{50}}}{D_{\mathrm{low}}\left(\frac{1}{\mathrm{TCP}_{\mathrm{low}}}-1\right)^{1/4\gamma_{50}}}=\left(\frac{\frac{1}{\mathrm{TCP}_{\mathrm{high}}}-1}{\frac{1}{\mathrm{TCP}_{\mathrm{low}}}-1}\right)^{1/4\gamma_{50}} \quad (2)$$

where subscripts high and low indicate the high- and low-FDG-uptake groups. In a trial, the dose prescription was not dependent on the FDG uptake group, and the D_{high} and D_{low} are the same. Also, the same γ_{50} value was assumed for both high- and low-FDG-uptake groups ($\gamma_{50,\mathrm{high}} = \gamma_{50,\mathrm{low}} = \gamma_{50}$).

The boost dose required for the high-FDG-uptake group to achieve the same TCP as the low-FDG-uptake group was estimated from the ratio of TD_{50} values ($TD_{50,high}/TD_{50,low}$). Since the same slopes (γ_{50}) were applied to both groups, the dose ratio between the two groups remains unchanged and is equal to the ratio of $TD_{50,high}/TD_{50,low}$ (mDMF) for any level of TCP. Therefore, the dose required for the high-FDG-uptake group can be estimated from the product of the prescribed dose and mDMF.

For whole-group analysis, a logistic regression was performed, based on the logistic TCP function. Appropriate weighting, based on standard error of population means, was applied to each clinical datapoint, as shown in the following equation:

$$w_i=\frac{1}{\sigma_i^2}=\frac{n_i}{p_i(1-p_i)} \quad (3)$$

where w_i is the weight of ith datapoint, σ_i is the standard error, p_i is the TCP, and n_i is the number of patients at the datapoint. The weight is proportional to the number of patients and increases as the TCP approaches either end (0 or 1).

Separate local control rates (high- vs. low-FDG-uptake groups) for each dataset were placed on the estimated equivalent dose (Fig. 1(d)). Then, a logistic regression was performed for each group with the same slope (γ_{50}) used for the equivalent dose estimation, in order to find the ratio of TD_{50} values between the two groups ($TD_{50,high}/TD_{50,low}$) and the resulting mDMF.

External validation with additional datasets

To further test the estimated mDMF, an additional analysis was performed with other datasets. We applied less restrictive inclusion criteria, such as: various FDG indices,

including metabolic tumor volume (MTV) or integrated SUV value; various outcome end-points, including disease-free survival (DFS), loco-regional control (LRC), or primary relapse-free survival (PRFS); and cohort groupings between high- and low-FDG-uptake groups by best cut-off. From the reviewed literature, seven studies with 329 patients were identified for the validation analysis [37–43], as shown in Supplementary Table 2. Through the same procedure as the original analysis, the TD_{50} ratio (mDMF) was estimated between high- and low-FDG-uptake groups. The mDMF for combined datasets (original and validation) was also evaluated.

Results

The outcome-equivalent dose was estimated for each dataset; it was based on the dose response curve generated by the logistic TCP function, resulting in an average TD_{50} value of 59.3 and an assumed γ_{50} value of 2 (as described in detail in the ‘‘Outcome-equivalent dose’’ section). Fig. 1 illustrates the method used to find the equivalent dose for each dataset. Since the average TD_{50} value was used in this method, compared to the nominal dose, half of the datasets had an increased equivalent dose and the other half had a decreased equivalent dose. The clinical data from our institution showed the greatest increase, by about 16%, of equivalent dose (81.3 Gy) from a nominal dose of (70 Gy), whereas Lin et al.’s data [26] showed the greatest decrease, by about 13%, of equivalent dose (61.4 Gy) from a nominal dose of (70.2 Gy).

For individual datasets, the boost dose required to compensate for a worse outcome probability, in the high-FDG-uptake group, was found from Eq. (2). The mDMF was estimated for three different γ_{50} values (γ_{50} = 1.5, 2, and 2.5), and the results are summarized in Supplementary Table 3. For individual clinical data, the estimated mDMFs were found to be in the range of 1.07–1.62, with a tendency to decrease as the presumed slope (γ_{50}) increased up to 2.5.

With γ_{50} = 2, which is thought to most likely represent the clinical reality, the derived mDMFs were in the range of 1.09–1.44 for each clinical datapoint. This implies that 9–44% of extra dose is required to compensate for the radioresistance of high-FDG-uptake tumors. Considering the prescribed dose was about 70 Gy, the total dose required for the high-FDG-uptake group is in the range of 76.3–100.8 Gy.

Considering all the data included in this study, the TCP curves for high- and low-FDG-uptake groups were evaluated by weighted logistic regression analysis for three different γ_{50} values (γ_{50} = 1.5, 2, and 2.5). The mDMFs are shown in the last row of Supplementary Table 3, and the regression plot is shown in Fig. 2 for γ_{50} = 2. The fitted curve for each group was consistent with the data based on the χ^2-test with *p*-values of 0.984 and 0.977 for high- and low-FDG-groups, respectively. The mDMF was 1.19 ± 0.08, which means the high-FDG-uptake group requires about 19% more dose to equalize the TCPs between low- and high-FDG-uptake groups.

For the external validation analysis, the mDMF was estimated to be 1.20 ± 0.04 assuming γ_{50} = 2, as shown in Supplementary Fig. 1. When combined with the original datasets, the

overall mDMF was estimated to be 1.19 ± 0.06, with p-values (from χ^2-test) of 0.998 and 1.00 for high- and low-FDG-groups, respectively (Fig. 3).

Discussion

Despite the well-known relationship between FDG-avidity and increased local failure, there has been no previous estimate of the boost dose required to offset adverse clinical outcomes in patients with FDG-avid tumors. In this work, the boost dose was estimated from available clinical outcome data. Assuming the same slope in the dose response curves for both groups (γ_{50} = 1.5, 2, or 2.5), the boost dose required for FDG-avid tumors to achieve the same TCP can be calculated directly from the ratio of $TD_{50,high}/TD_{50,low}$ for any TCP.

For all the datasets, the mDMF was estimated to be 1.19 for γ_{50} = 2, from the weighted logistic regression, which implies an extra 19% of dose is needed for FDG-avid tumors. For example, assuming a non-boost dose of 70 Gy, the most likely boost dose to equalize the tumor control rate with FDG-non-avid tumors would be approximately 83 Gy. Considering the possible variation of the γ_{50} value (1.5–2.5), boost doses might range between 80 Gy and 88 Gy.

To our knowledge, this is the first estimation from clinical outcomes of the boost dose required for FDG-avid tumors, even though several dose escalation studies have arbitrarily adopted about 10–35% of extra dose for high FDG-PET sub-volumes [22,23,44]. The result of this study provides clinical evidence of the range of boost dose required to compensate for the FDG-avidity. These boost doses have been shown to be feasible in these patients with acceptable increases in NTCP, as shown by Lee et al. [45] in the context of tumor hypoxia dose escalation.

The weighted-mean difference of the SUV_m values between high- and low-FDG-uptake groups (ΔSUV_m) was evaluated to be 8.7, from which the extra dose required to neutralize a one-unit increase of SUV_m can be interpreted to be about 2.2%/SUV_m (γ_{50} = 2), which is equivalent to 1.5 Gy/SUV_m for a non-boost dose of 70 Gy (see Supplementary materials for detail).

In order to analyze heterogeneous multi-institutional datasets, we introduced a general method. The overall outcome of each dataset was normalized in a single dose response curve, which was derived from the average TD_{50} value of all the datasets and a clinically relevant slope (γ_{50}), and the outcome-equivalent dose was derived for each dataset. Although the nominal prescribed doses were not significantly different (~70 Gy), the outcomes were considerably different among the trials, and the estimated equivalent dose varied significantly. This variation seems to reflect the effects of other prognostic factors, such as T-stage, chemotherapy, HPV status, and treatment technique, which varied significantly among datasets. The ratio of equivalent dose to nominal dose was between 0.87 and 1.16. This method is applicable to studying many other factors that modify the dose response curve, such as age, stage, etc.

Several potential confounding factors must be recognized in this dataset. First, not all patients received chemotherapy, which has been shown in multiple studies to be an

important contributor to increased overall survival. Second, these tumors consist of a heterogeneous group of head and neck cancer patients ranging from clinically radioresistant oral cavity cancers to the more favorable tumors such as cancer of the oropharynx. Third, different T-stages have been correlated with outcome, i.e., higher stage tumors do worse than lower stage tumors [23,25], but this was not explicitly accounted for in our dataset. In our overall logistic analysis, the greater the fraction of patients with lower T-stage (T1–2), the higher the estimated equivalent dose was (Supplementary Fig. 2), as expected. Lastly, human papilloma virus (HPV) has recently been recognized as probably the most important biomarker that predicts tumor response in head and neck cancer [46,47]. Due to the nature of meta-analysis and the lack of tissue confirmation, however, detailed evaluation of each factor was not possible. We judge that the outcome-equivalent dose could account for those confounding factors to a certain degree. Further analyses that takes into account these factors is required to shed more light on the impact of FDG uptake alone apart from tumor volume, HPV status, etc.

The sensitivity of the estimated TD_{50} ratio was tested on a range of parameter values in the derivation of outcome-equivalent dose. As shown in Supplementary Table 4, the variation of the TD_{50} value used in equivalent dose estimation does not affect the estimated TD_{50} ratio and resulting boost dose for FDG-avid tumors, since the ratio is preserved for any TCP. Variation of the γ_{50} value had a modest impact on the estimation of the TD_{50} ratio and variations of ±10% yielded a change of less than 2%.

In order to further test the robustness of the estimated mDMF, we identified seven additional studies ($n = 329$), based on less restrictive criteria: FDG index (SUV_m or MTV); outcome end-point (DFS, LRC, or PRFS); and cohort grouping (median or best cut-off). From the validation datasets, the mDMF was evaluated to be 1.20, which is almost the same as the original analysis (1.19). Also, the combined analysis yielded the same overall mDMF as the original analysis (Fig. 3). Although there should be inevitable differences between the two datasets, due to the different criteria applied to the validation dataset, this additional analysis supports the methodology of the study.

In this study, the slope of the dose–response curve was assumed to be the same for both high- and low-FDG-uptake groups. However, this might not always hold, as Schütze et al. showed in their pre-clinical study [48]. They investigated the effect of increased radiation dose on local control depending on FDG uptake for FaDu tumors in nude mice and concluded that the high FDG-uptake group has a steeper dose response. To test for the effect of variable slopes, we repeated the logistic regression with the γ_{50} value as a free variable (Supplementary Fig. 3). This yielded a result with a slightly steeper dose response for the low-FDG-uptake group. This difference with the results of Schütze et al. might be caused by the difference in host (animal vs. human) or by the difference in fractionation (single dose vs. standard fractionation). Further investigations are warranted to confirm the relationship between the slope of the dose–response curve and FDG-avidity.

Publication bias for the current study was tested with a funnel plot. In the plot, it is assumed that the studies having lower uncertainty with larger sample size tend to represent the true value, while smaller studies with larger uncertainty tend to spread on both sides of the true

value. An asymmetry in the plot implies possible publication bias in the study. In our study, the distribution at larger standard error seems to be asymmetric, which might be indicative of publication bias (Supplementary Fig. 4). Our work is based on published literature and all the studies included have statistically significant differences in outcome between high- and low-FDG-uptake groups. Although some authors reported non-significance [49,50], studies that failed to achieve statistical significance might not be published, leading to an overestimation of the effect.

In spite of several limitations, this study provides a feasible approach to derive a prescription function from clinical data, resulting in a consistent estimate. For a better estimation of the boost dose required to compensate for FDG avidity, a more detailed study with a larger dataset is warranted, controlling other confounding factors, such as primary tumor site, tumor size, chemotherapy, and HPV status.

Methodologically, we have introduced an entirely new analysis method, based on finding the ‘outcome-equivalent dose’ for each analysis cohort. The importance of this general tool is that it can be used to estimate dose-modifying effects due to any risk factors across heterogeneous cohorts. One example might be the estimation of the dose-modifying factor of hypoxia. With the increasing use of hypoxia-specific PET imaging such as FISO, Cu-ATSM, and FAZA in clinical applications [51–53], a similar analysis might be performed for an improved RT strategy to deal with hypoxia.

Conclusion

In this work, the relationship between FDG-avidity and tumor radiosensitivity was explored. We introduced a novel analysis method that accounts for inter-institutional differences in non-FDG factors, such as treatment planning, delivery, and tumor characteristics, allowing for a direct estimate of the dose response modifying effect of variation in FDG uptake. The method assumes that the impact of the risk-factor (in this case FDG-avidity) has a similar dose-modifying effect across heterogeneous cohorts. Although this is not necessarily true *a priori*, curve fitting chisquare tests show that it is a useful approximation in this case. The range of extra dose required for FDG-avid tumors was estimated from clinical data. To reach equal response rates, FDG-avid tumors are likely to require at least 10–30% more dose than FDG-non-avid tumors. These estimates provide a rational starting point for clinical trials to test the usefulness of IMRT boost for FDG-avid tumors. However, due to the confounding effect of tumor volume/ T-stage, and other prognostic factors, independent tests of the estimated dose-modifying effect, using high-quality prospective clinical trial data, are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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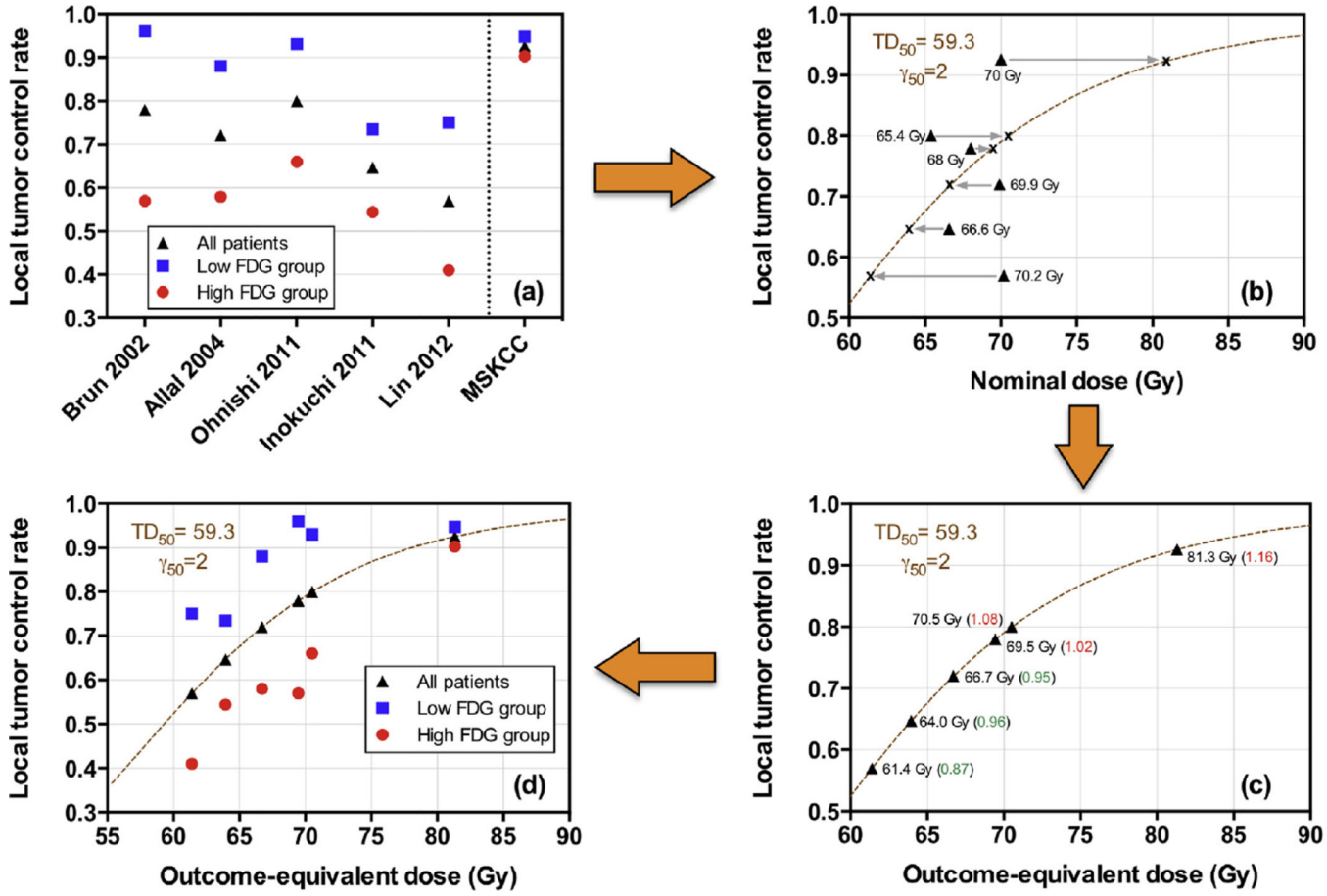

Fig. 1.

The estimation of outcome-equivalent dose: (a) the local control rates of the high-FDG group (red circles), low-FDG group (blue squares), and all patients (black triangles) for each clinical outcome data; (b) a representative logistic dose response curve estimated from the overall local control rate for all the datasets (TD_{50} = 59.3 Gy for γ_{50} = 2); (c) the equivalent dose estimated for each clinical data by aligning the total local control rate with the representative dose response curve (with the ratio of equivalent dose to nominal dose in each parenthesis); and (d) the local control rates for high- and low-FDG groups for each clinical data at the estimated equivalent dose, from which the TD_{50} value for each group and the ratio $TD_{50,high}/TD_{50,low}$ were estimated based on logistic regression.

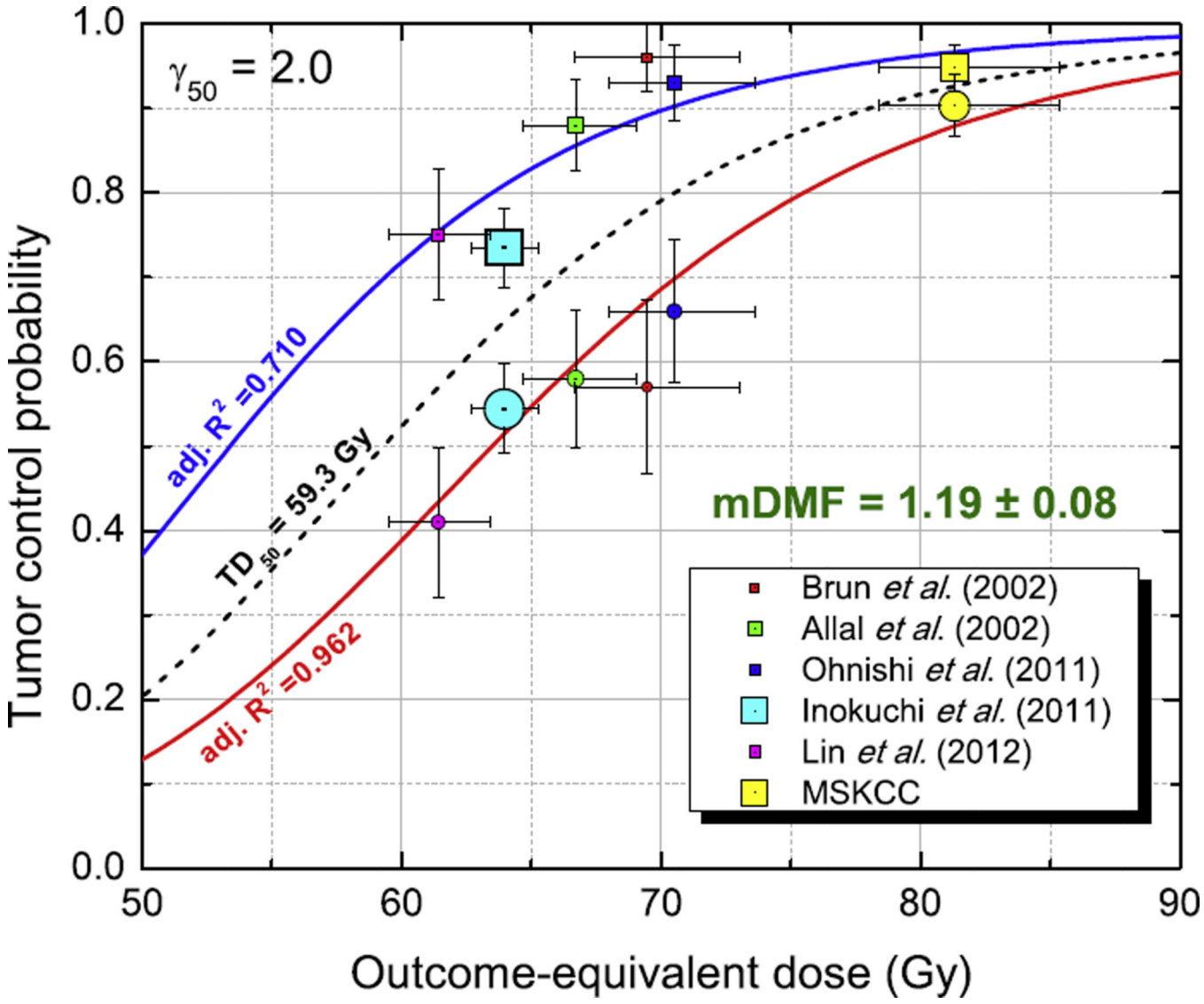

Fig. 2.

Tumor control probability (TCP) curves for high- (circles; red line) and low-(squares; blue line) FDG-uptake groups, evaluated by weighted logistic regression analysis with a mDMF value for γ_{50} = 2. Note that the size of each datapoint (square or circle) corresponds to the size of the study and the error bar indicates one standard error (1σ) for each data point. The x-error bar was estimated from the conversion of the standard error of the total local control rate into the uncertainty of the equivalent dose.

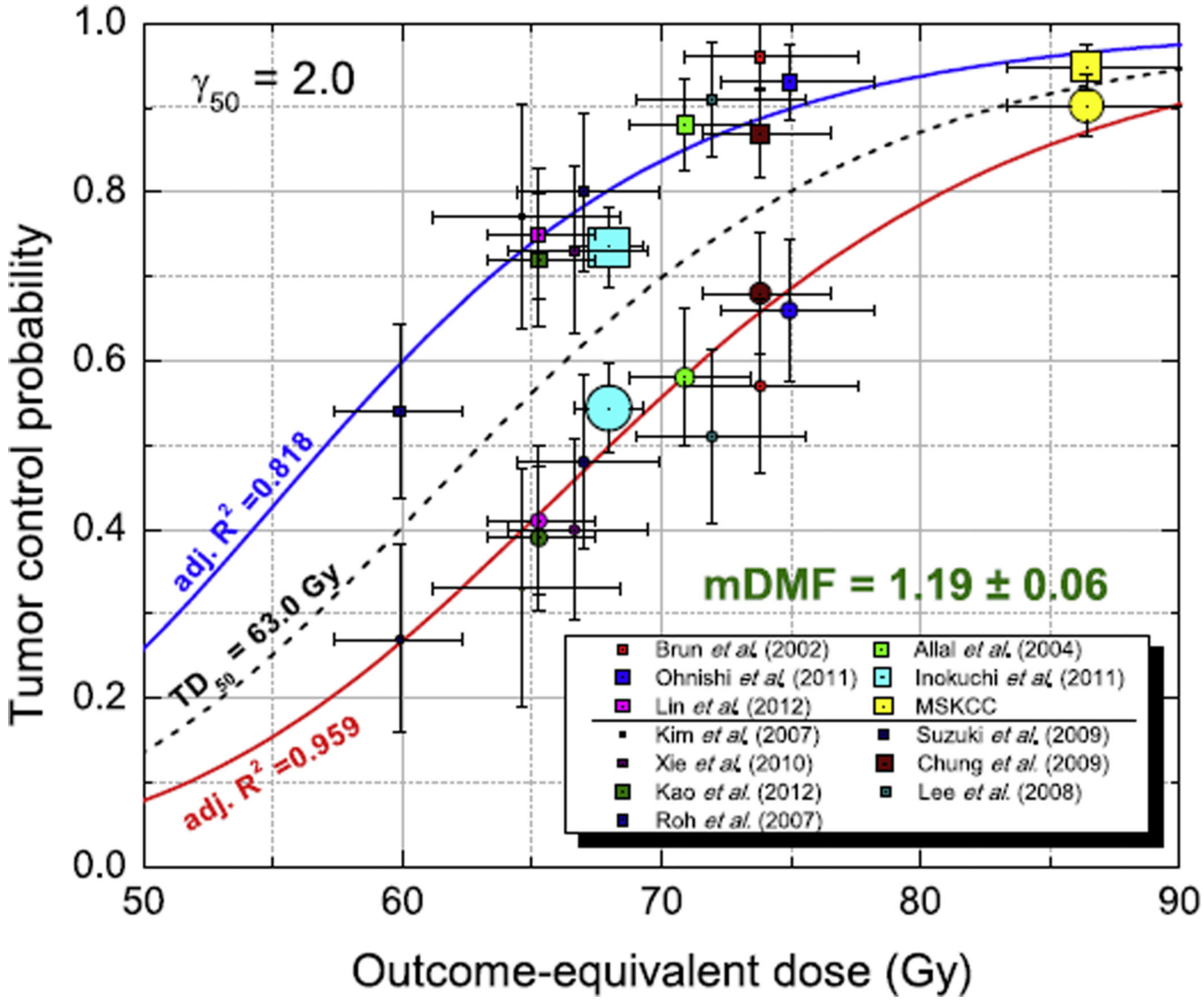

Fig. 3.

Combined analysis of both original and validation datasets for the estimation of mDMF with γ_{50} = 2.

Table 1

Characteristics of internal validation dataset of oropharynx cancer patients treated with definitive radiation therapy at MSKCC (n = 135).

Characteristics	Total	High FDG (SUV_m > 13.9)	Low FDG (SUV_m ≤ 13.9)	p-Value*
# of patients	135	67	68	
Gender (M/F)	117/18	57/10	60/8	0.589
Median age [range] (years)	57 [28–84]	58 [39–84]	57 [27–84]	0.735
Sub-site of primary tumor (in oropharynx)				0.118
Base of tongue	66	37	29	
Tonsil	62	28	34	
Soft palate	3	2	1	
Pharyngeal wall	4	0	4	
T-stage				0.026
T1	12	1	11	
T2	63	34	29	
T3	32	16	16	
T4	28	16	12	
N-stage				0.396
N0	10	3	7	
N1	27	15	12	
N2	94	48	46	
N3	4	1	3	
Overall stage				0.772
II	3	1	2	
III	26	14	12	
IV	106	52	54	
Histologic grade				0.500
G1	1	1	0	
G2	48	25	23	
G3	71	32	39	
Unknown	15	9	6	
KPS score				0.802
70	1	1	0	
80	16	8	8	
90	87	42	45	
100	23	11	12	
Unknown	8	5	3	
Median SUV_m [range]	13.9 [3.4–28.2]	16.9 [14.1–28.2]	9.4 [3.4–13.9]	–
Median primary RT dose [range] (Gy)	70.0[67.8–70.0]	70.0[67.8–70.0]	70.0[69.9–70.0]	0.907
Median RT duration [range] (day)	45 [37–77]	45 [37–65]	45 [39–77]	0.993
Chemotherapy				0.261

Characteristics	Total	High FDG (SUV_m > 13.9)	Low FDG (SUV_m ≤ 13.9)	*p*-Value*
Concurrent	127	64	63	
Concurrent + Neoadjuvant	4	2	2	
Concurrent + Adjuvant	1	1	0	
None	3	0	3	
Median follow-up [range] (month)	33.1 [2.0–80.9]	33.1 [2.0–80.9]	33.5 [4.0–73.6]	0.671

*Comparison between high- and low-FDG-uptake groups: χ^2-test, except for age, SUV_m, RT dose, RT duration, and follow-up period (*t*-test).

Table 2

Datasets included in this study.

Clinical data	Site	SUV_m cut-off (median)	# of patients	Local control (%)			RT Dose (Gy)
				Total	Each group	Follow-up interval(log-rank test)	
Brun et al. [25]	Head and neck	≥9.0	23	78	57	5-year	68
		<9.0	23		96	(p = 0.003)	(66–70)
Allal et al. [26]	Head and neck	≥5.5	37	72	58	4-year	69.9
		<5.5	36		88	(p = 0.01)	(69.8–74.4)
Ohnishi et al. [27]	Oropharynx/hypopharynx	≥12.0	32	80	66	2-year	65.4
		<12.0	32		93	(p = 0.024)	(61.4–71.4)
Inokuchi et al. [28]	Head and neck	≥12.25	89	64.7	54.4	3-year	66.6
		<12.25	89		73.5	(p = 0.03)	(30–120)
Lin et al. [29]	Oropharynx/hypopharynx	>11.0	31	57	41	3-year	70.2
		≤11.0	31		75	(p = 0.003)	(68.4–73.8)
Internal validation (MSKCC)	Oropharynx	>13.9	67	92.6	90.3	5-year	70.0
		≤13.9	68		94.8	(p = 0.258)	(67.8–70.0)