Original Article

Predictive Models of Toxicity With External Radiotherapy for Prostate Cancer

Clinical Issues*

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The objective of the current study was to analyze the state of the art and present limitations of available predictive clinical models (when available) estimating the risk of genitourinary tract and small bowel complications, erectile dysfunction, and acute and late symptoms of the rectal syndrome caused by prostate cancer external irradiation. An analysis of the literature indicated that very limited attention has been devoted to the development of "integrated," patient-tailored, user-friendly, and clinically usable tools for the prediction of external beam radiotoxicity. In this article, the authors reported on the multivariate correlation between late genitourinary and gastrointestinal toxicities and clinical/dosimetric risk factors, as well as on the first set of nomograms developed to predict acute and late rectal side effects. At the present state of knowledge, the use of nomograms as predictive instruments of radiotoxicity appears to be particularly attractive for several main reasons. They are "user friendly" and easily developed using the results of multivariate analyses, as they weigh the combined effects of multiple independent factors found to be correlated with the selected clinical endpoint. The integrated evaluation of clinical and dosimetric parameters in the single patient can help to provide a tailored probability of the specific outcome considered. Predicting a high probability of toxicity could avoid unnecessary daily costs for the individual patient in terms of quality of life modification during and after treatment, helping patients in the decision-making process of choosing the best individual, quality of life–related treatment, and clinicians in better tailoring the treatment to patient's characteristics. **Cancer 2009;115(13 suppl):3141–3149. © 2009 American Cancer Society.**

KEY WORDS: prostate cancer, radio-induced toxicity prediction, conformal radiotherapy, nomograms.

In the recent years, there has been growing interest among radiation oncologists in developing predictive models of practical utility (ie, probability formulas and nomograms) in prostate cancer irradiation. Nearly all have been focused on disease control prediction (to help physicians and to counsel patients in the decision-making process),[1-5] on the prediction of pathologic extension (to select anatomic target[s] for external

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Table 1. Clinical Factors Found to Be Correlated With Late Genitourinary Toxicity (Organ: Bladder; Endpoint: Late Genitourinary Toxicity)

Study	No. of Patients	Clinical Risk Factor	Stratification	Hazard Ratio	*P*	Endpoint
Peeters 2005[14]	669	Prior TURP	Yes vs no	1.7	<.01	RTOG/EORTC grade ≥2
Peeters 2005[14]	669	Prior TURP	Yes vs no	3.1	<.01	RTOG/EORTC grade ≥3
Peeters 2005[14]	669	Androgen deprivation	Yes vs no	2.2	<.01	RTOG/EORTC grade ≥2
Peeters 2005[14]	669	Androgen deprivation	Yes vs no	2.3	.03	RTOG/EORTC grade ≥3
Peeters 2005[14]	669	Pretreatment GU symptoms	Grade ≥2 vs grade <2	2.2	<.01	RTOG/EORTC grade ≥2
Zelefsky 2008[15]	1571	Acute toxicity	Grade ≥2 vs grade <2	3.2	<.01	CTCAE grade ≥2
Cahlon 2008[16]	478	Pre-RT GU medication	Yes vs no		<.01	CTCAE grade ≥2
Cahlon 2008[16]	478	Age	<70 y vs ≤70 y		<.01	CTCAE grade ≥2

TURP indicates transurethral resection of the prostate; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GU, genitourinary; CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy.

beam radiation therapy [EBRT][6-8]), on supporting radiation oncologists in the decision of dose levels to be delivered,[9] and on helping clinicians choose the appropriate combination of therapies both in standard practice (ie, neoadjuvant/adjuvant androgen suppression)[3,10] and in experimental clinical trials (ie, chemotherapy for high-risk patients[11] as in the Radiation Therapy Oncology Group [RTOG] 0521 study and in the Dana-Farber Cancer Institute Protocol 05-043).

Curiously, very limited attention and inadequate efforts have been devoted to the development of "easy to use" tools for the prediction of probability of radiation side effects in the individual patient.

Predicting radiation morbidity is of great importance because it can prevent unnecessary worsening of quality of life for the individual patient, and can help in introducing planning corrections to better personalize radiation treatments.

The objective of the current study was to analyze the state of the art and present limitations of available clinically usable models predicting the risk of genitourinary (GU) tract and bowel complications, of erectile dysfunction, and of acute and late symptoms of the rectal syndrome (lower gastrointestinal [LGI]) caused by prostate cancer external irradiation.

GU Complications

Few studies exist in the literature clarifying the role of clinical-dosimetric variables affecting the risk of developing symptoms and signs of the GU syndrome; no user-friendly predictive tool is currently available to assist clinicians in the prediction and minimization of such radiation sequelae. Furthermore, information regarding clinical variables potentially affecting GU toxicity is lacking, with only limited data on dosimetric factors being known.[12,13] Results on factors involved in conditioning GU morbidities are still controversial, as can easily be deduced from 3 recently reported large analyses. Peeters et al (multicenter Dutch randomized trial)[14] found prior transurethral resection of prostate, androgen deprivation therapy, and pretreatment GU symptoms (but no dose influence) all statistically related to late RTOG/European Organization for Research and Treatment of Cancer (EORTC) urinary toxicity, whereas Zelefsky et al (Memorial Sloan Kettering Cancer Center [MSKCC] Group 3-dimensional conformal radiation therapy [3DCRT] + intensity-modulated radiation therapy [IMRT] patients)[15] found radiation dose (<81 grays [Gy] vs >81Gy) and acute toxicity (grade 0-1 vs 2-4) to be the only variables significantly conditioning late GU morbidity. Cahlon et al (MSKCC Group IMRT patients)[16] found GU medications before IMRT and age >70 years to be significantly correlated with the presence of grade ≥2 late morbidity. Table 1 summarizes the major findings (on late GU toxicity) from selected studies.

These difficulties, most likely also related both to the maintaining of similar bladder filling within the same study and to different instructions for bladder filling among different studies, clearly explain why prediction tools are lacking; only 1 model exploiting artificial neural networks (ANNs)[17] has been published to date, which partially and theoretically addressed the issue of prediction of radiation-induced bladder toxicity. Specifically,

the ANN model predicts grade 2-3 nocturia, including bladder volume, prescribed dose, margins between clinical target volume (CTV) and planning target volume (PTV), and dose volume histogram (DVH) information to be significant technical-dosimetric factors.

It is evident that to clarify this issue, new trials focused on clinical as well as dosimetric factors affecting the GU syndrome should be specifically designed, thus facilitating the construction of predictive tools to better tailor treatments to the individual patient.

Bowel Complications

Acute and late radiation enteropathy is an issue when prostate cancer radiotherapy involves lymph node irradiation. The existence of a large dose-volume effect for bowel is well assessed from clinical evidence,[18,19] and quantitative dose-volume relationships for this endpoint are discussed elsewhere in this supplement. When considering clinical risk factors, an investigation recently conducted at the San Raffaele Institute (on a population of 191 patients) showed a correlation between acute bowel toxicity and previous abdominal surgery[20] (odds ratio = 2.4; $P = .05$). This point is in agreement with Huang et al,[21] who found a higher risk in gynecological patients previously submitted to abdominal surgery.

These points constitute only initial knowledge of the factors affecting bowel morbidity, and further studies are needed to develop predictive tools that might help in minimizing the insurgence of radiation enteropathy.

Erectile Dysfunction

As well as bowel and GU morbidities, factors influencing the occurrence of postradiation erectile dysfunction have not yet been adequately studied and understood. No studies performed to date in prostate cancer patients undergoing radiation have thoroughly analyzed the possible influence of patients' previous medical history, comorbidities, and related drug consumption and tumor stage, or attempted to discriminate the influence of the disease or of psychologic burden in estimating the risk of erectile dysfunction in patients undergoing watchful waiting or active surveillance. This issue is further complicated by the lack of evidence-based knowledge of the anatomical regions involved in the expression of erectile dysfunction. If several clues point to the penile bulb as the true target for radio-induced erectile dysfunction, other anatomic regions that appear to to play a major role in achieving an erection have also been considered, such as the neurovascular bundles, the crura, and the corpora cavernosa.

A very interesting point comes from recent data on genes predicting erectile dysfunction. Peters et al[22] found that the possession of certain transforming growth factorβ1 genotypes is associated with the development of erectile dysfunction. Therefore, the individuation of patients harboring these genotypes may represent a means of identifying men who could have poor quality of life after EBRT for prostate cancer.

Rectal Complications

The role of dosimetric variables influencing rectal toxicity appears to be quite well understood. A solid set of dose volume constraints (V40Gy → V75Gy) and logistic curves estimating the risk of rectal injury associated with these constraints are readily available in the literature and routinely used in clinical practice.[14,23-28] More sophisticated tools are also accessible, such as those that reduce all DVH information to the Equivalent Uniform Dose and those using normal tissue complication probability (NTCP) models.[29-31] A detailed discussion of dosimetric predictors of the rectal syndrome is provided elsewhere in this supplement.

In dealing with the role of clinical variables, a more complex scenario appears. Recent studies on large, prospectively followed populations have established clear evidence of the negative impact on late rectal side effects of both abdominal surgery before EBRT[14,27] and acute LGI toxicity,[14,15,32] as well as the protective effect of hormonal treatment (because of prostate downsizing) on acute LGI toxicity.[14,33] However, several clinical factors still need to be fully understood: no consensus exists on the true influence of diabetes and related drugs,[27] of hypertension and related drugs, of the concomitant use of anticoagulants and antiaggregants, on the role of androgen deprivation,[32,34-36] or on the exact impact of hemorrhoids on late rectal morbidity. Table 2 summarizes the major findings (on late rectal bleeding) from selected studies.

Last but not least, the possible influence on toxicity of individual genetic susceptibility to radiation is still in

Table 2. Clinical Factors Found to Be Correlated With Late Rectal Bleeding (Organ: Rectum; Endpoint: Late Rectal Toxicity [Bleeding])

Study	No. of Patients	Clinical Risk Factor	Stratification	Hazard Ratio	*P*	Endpoint
Feigenberg 2005[35]	1204	Androgen deprivation	>6 mo vs ≤6 mo	1.3	<.01	Modified Fox Chase grade ≥2
Sanguineti 2002[34]	182	Androgen deprivation	Yes vs no	2.2	.02	RTOG grade ≥2
Vargas 2005[32]	331	Acute lower GI toxicity	Yes vs no	2.1	.005	RTOG grade ≥2
Peeters 2005[14]	553	Acute proctitis	Yes vs no	1.5	.01	Intermittent bleeding
Peeters 2005[14]	553	Acute mucous discharge	Yes vs no	1.6	.001	Intermittent bleeding
Zelefsky 2008[15]	1571	Acute toxicity	Grade ≥2 vs grade <2	6.95	<.01	Late GI toxicity, CTCAE grade ≥2
Cahlon 2008[16]	478	Acute lower GI toxicity	Grade ≥2 vs grade <2		<.01	Late GI toxicity, CTCAE grade ≥2
Peeters 2005[14]	641	Abdominal surgery	Yes vs no	2.7	<.01	Bleeding requiring laser or transfusion
Fiorino 2008[27]	506	Abdominal surgery	Yes vs no	4.4	.06	Bleeding requiring laser or transfusion more than twice weekly

RTOG indicates Radiation Therapy Oncology Group; GI, gastrointestinal; CTCAE, Common Terminology Criteria for Adverse Events.

the "Stone Age" and should be elucidated because, given the same set of clinical/dosimetric factors, patient-to-patient variability in normal tissue response to radiation has been widely recognized in clinical practice, suggesting that this phenomenon might be, at least in part, genetically driven.

Predictive Models Integrating Clinical and Dosimetric Information

There is only 1 paper published to date in which a user-friendly, clinical/dosimetric predictive radiotoxicity tool (estimating the risk of acute LGI side effects after conformal irradiation for prostate cancer) was used.[37] In this article, a set of nomograms were proposed as instruments to estimate the risk of acute rectal toxicity. Four endpoints were considered: 1) G2-G3 RTOG/EORTC LGI toxicity (Fig. 1), 2) moderate/severe rectal bleeding (Fig. 2), 3) severe fecal incontinence (Fig. 3), and 4) moderate/severe increased stool frequency (Fig. 4). All nomograms were developed on the basis of a large database (1132 patients) derived from the Italian multicenter AIROPROS 0102 trial.[27,33] It was specifically focused on trying to elucidate potential variables affecting the radio-induced rectal syndrome using a prospective evaluation of both RTOG/EORTC LGI morbidity and a self-reported questionnaire analyzing several symptoms of the rectal syndrome. These nomograms, even if not yet validated on independent sets of patients, constitute an initial tool with which to assess the single-patient probability of exhibiting acute LGI morbidity. It is worth remembering that late GI toxicity

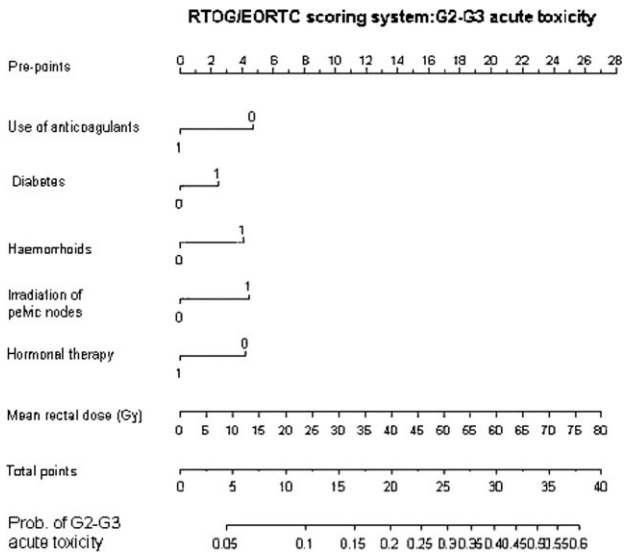

FIGURE 1. A nomogram for moderate/severe Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) lower gastrointestinal acute toxicity is shown. G2/G3 indicates grade 2/grade 3; Gy, grays; Prob., probability. Reprinted from Valdagni R, Rancati T, Fiorino C, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71:1065-1073, with permission from Elsevier.

has been widely recognized as 1 of the most important radiation-induced morbidities, as it presents in a significant proportion of irradiated prostate cancer patients and may persist for several years after the completion of radiotherapy. Nonetheless, moderate/severe acute gastrointestinal side effects, even if typically transient in nature, can occur in approximately 25% of patients (25.9% in our

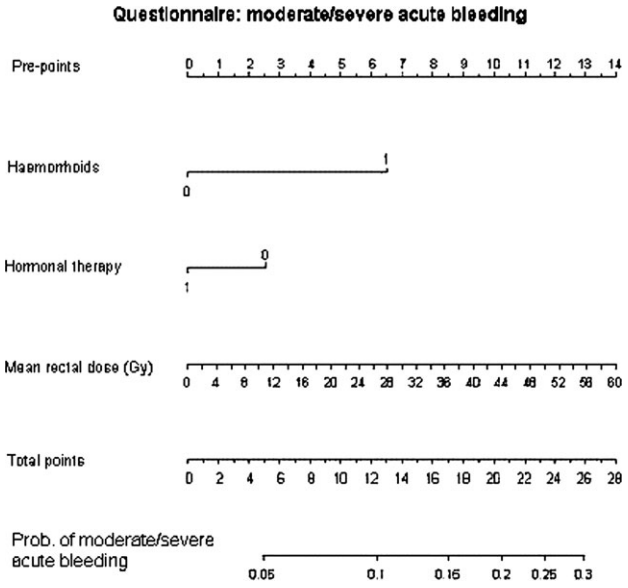

FIGURE 2. A nomogram for moderate/severe acute rectal bleeding is shown. Gy indicates grays; Prob., probability. Reprinted from Valdagni R, Rancati T, Fiorino C, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71:1065-1073, with permission from Elsevier.

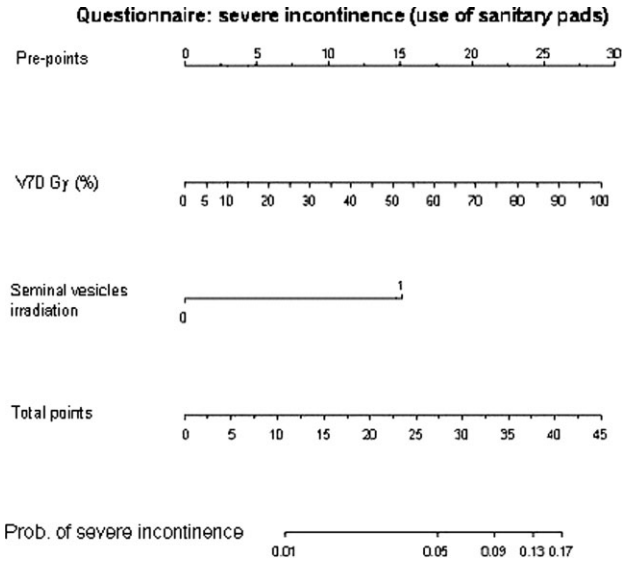

FIGURE 3. A nomogram for severe acute fecal incontinence is shown. Gy indicates grays; Prob., probability. Reprinted from Valdagni R, Rancati T, Fiorino C, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71:1065-1073, with permission from Elsevier.

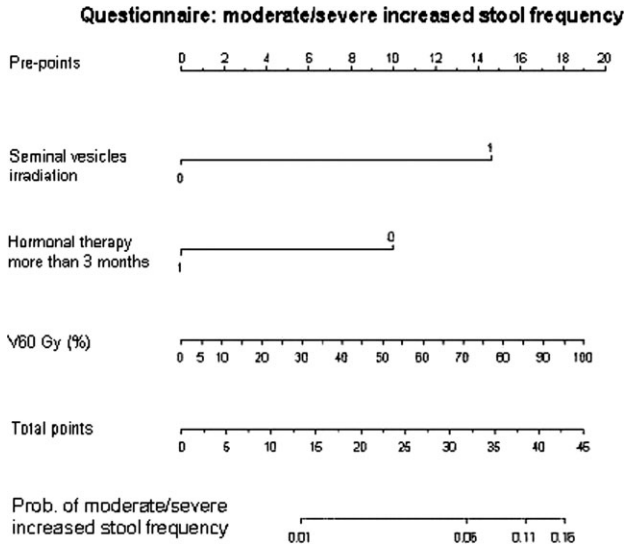

FIGURE 4. A nomogram for moderate/severe acute increased bowel frequency is shown. Gy indicates grays; Prob., probability. Reprinted from Valdagni R, Rancati T, Fiorino C, et al. Development of a set of nomograms to predict acute lower gastrointestinal toxicity for prostate cancer 3D-CRT. *Int J Radiat Oncol Biol Phys*. 2008;71:1065-1073, with permission from Elsevier.

experience[33]), and there is mounting evidence that acute damage plays a significant role in late toxicity.[14,32] Consequently, the highly probable prediction of acute toxicity could avoid unnecessary daily costs for the individual patient in terms of quality of life modification during treatment and possibly afterward, and could help clinicians in better tailoring the treatment to patient characteristics.

With respect to late toxicity, to date, only 1 model exploiting ANNs has been published to date.[17] This ANN model helps to predict G2-G3 late rectal bleeding and includes rectal volume, prescribed dose, margins between CTV and PTV, and DVH information as significant technical-dosimetric factors.

With respect to nomogram prediction of late LGI toxicity, no published data are yet available. Data from 615 patients of the AIROPROS 0102 trial with a minimum follow-up of 36 months are now becoming available, and a set of nomograms predicting late morbidity will be the object of a future publication. Figure 5 shows the first of these nomograms, which predicts the risk of G2-G3 late rectal bleeding. In multivariate logistic analysis, V75Gy was found to be significantly correlated with G2-G3 late rectal bleeding, together with abdominal

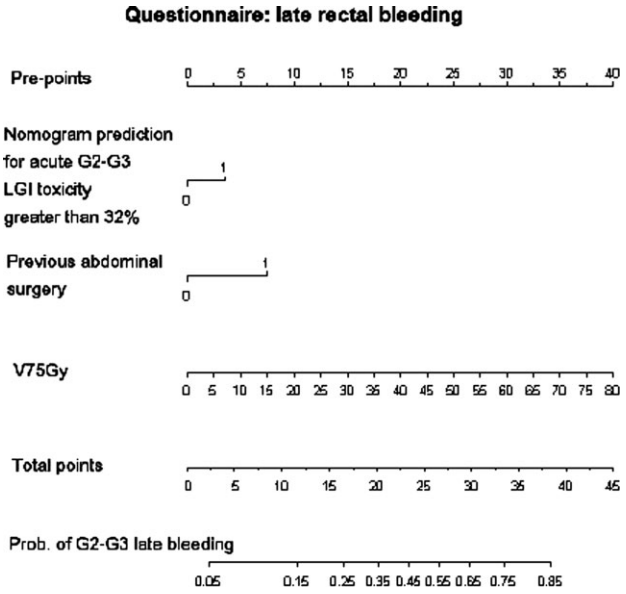

FIGURE 5. A nomogram for grade 2 to 3 late rectal bleeding is shown. G2-G3 indicates grade 2-3; LGI, lower gastrointestinal; Gy, grays; Prob., probability.

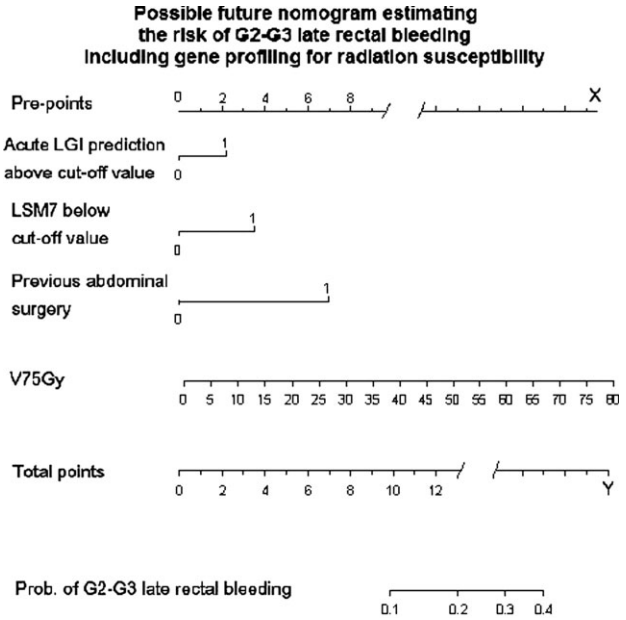

FIGURE 6. A hypothetical nomogram for the prediction of late rectal bleeding is shown, with inclusion of the single-patient *LSM7* expression for radiosensitivity. G2-G3 indicates grade 2-3; LGI, lower gastrointestinal; Gy, grays; Prob., probability.

surgery before conformal irradiation and the presence of G2-G3 acute LGI toxicity. To develop a pretreatment nomogram estimating G2-G3 late rectal bleeding and considering the significant correlation between acute and late LGI morbidity, the nomogram predicting acute LGI G2-G3 RTOG/EORTC acute toxicity (Fig. 1) was included in the nomogram predicting G2-G3 late rectal bleeding. With this substitution, V75Gy together with abdominal surgery before EBRT and predicted acute LGI toxicity (dichotomized variable: cutoff value = 32%) are used for the single patient evaluation of late rectal bleeding probability.

Predictive Models Integrating Clinicodosimetric and Genetic Information

Current radiotherapy practice is based on the assumption that the human population is uniform in its radiation sensitivity, with limited and dramatic exceptions being well recognized (ataxia telangiectasia, Fanconi anemia, Nijmegen breakage syndrome). However, there are several indications from human studies suggesting that this assumption regarding uniform radiosensitivity is incorrect. It is also evident that, despite the utilization of highly sophisticated technology and the strict application of dose constraints, 3% to 10% of our patients still show evidence of moderate/severe rectal injury. Very few studies in the literature attempt to identify biological predictors of acute/late toxicity in prostate cancer irradiation, or examine the potential correlation between rectal injury, dosimetric variables, clinical factors, and the individual gene profile in the single patient. Data on genes influencing late rectal bleeding have recently become available,[38-41] but knowledge of the impact of gene expression profiling on radiotoxicity remains at a very primitive stage. To date, there exists no predictive tool that includes genetic information. Nonetheless, it is highly reasonable to expect that, in the near future, nomograms incorporating the genetic makeup of the single patient may become clinically relevant for the better individualization of radiation treatment for the individual patient. Figure 6 shows such a hypothetical nomogram, derived from AIROPROS 0102 data[27,33] and predicting late rectal bleeding. The inclusion of *LSM7* expression (the real weight on toxicity predictions is unknown) was made on the basis of the recent results of a pilot study[39] that identifies several genes potentially predictive for rectal toxicity. In the near future, genetic composition may be routinely combined with dosimetric and clinical variables to fully assess patient risk

of radio-induced toxicity, and nomograms may thus include genetic as well as dosimetric and clinical information.

DISCUSSION

In the last decade, several investigators in the field of prostate cancer irradiation have developed and applied "individualized" predictive tools (such as probability formulas and nomograms), as well as "nonindividualized" tools (such as risk classes), to estimate the risk of disease failure/control in its various clinical endpoints or surrogates, to better select targets for external radiation, to decide radiation dose, and lastly, to suggest the optimal combination therapy (eg, androgen deprivation).

Nonetheless, the study of predictors of radio-induced morbidity has been relegated essentially to an evaluation of the role of dosimetric variables, with the integration of clinical variables in predictive models only recently gaining the attention of the radiation community. When organs at risk of developing radiation sequelae are considered, an analysis of the literature reveals that most efforts to elucidate the influence of toxicity factors have been oriented toward analyzing variables that estimate the risk of rectal morbidity, with information on bladder, urethra, bowel, and anatomic regions causing erectile dysfunction being very scarce or limited to dosimetric data only.

Several reports using uni-/multivariate (logistic/actuarial) analysis are available for an estimate of the risk of gastrointestinal (and to a very minor extent, GU) complications. Studies regarding radio-induced rectal morbidity, although providing a solid set of dose-volume constraints to be observed to keep the probability of such morbidity reasonably low, do not definitively clarify the role of some clinical variables (such as the presence of diabetes or hypertension, or the use of concomitant androgen deprivation). For this reason, the predictive accuracy of these models may be limited, because in general they rely heavily on dosimetric variables, whereas other important factors (eg, comorbidities, concomitant use of drugs) are either not globally taken into account, or not yet understood (eg, genetic variables). Only recently, 2 large prospective investigations (the Dutch trial[14] and the Italian trial AIROPROS 0102[27,33]) were conducted with the specific goal of analyzing the correlation between clinical and dosimetric variables and the symptoms of the so-called rectal syndrome. Data derived from AIROPROS 0102 incorporating dosimetric as well as clinical information have allowed the development of the first set of nomograms predicting several symptoms of the acute rectal syndrome[37] and the first nomogram regarding late rectal bleeding. Other nomograms estimating the risk of several clinical events of late rectal toxicity in the individual patient are in the process of being developed.[42]

It must be emphasized that only preliminary data exist on the potential influence of individual genetic susceptibility to radiation injury,[38-41] but interpatient variability in normal tissue response to radiation suggests that in the near future, the genetic makeup of the individual patient will be incorporated in predictive modeling.

Conclusions

Predicting a high probability of toxicity could avoid unnecessary daily costs to the single patient in terms of quality of life modification during and after treatment, helping patients in the decision-making process, and clinicians in better tailoring the treatment to patient characteristics. Specifically, radiation oncologists might consider modifying: 1) treatment planning, introducing more stringent DVH constraints to have a reasonably lower risk of the specific endpoint considered; and/or 2) the treatment technique, shifting for example from 3DCRT to IMRT or image-guided radiation therapy; and/or 3) the radiation strategy (eg, adding, in selected cases, hormonal therapy to a lower prescription dose). Lastly, it could facilitate clinicians in counseling and directing the patient with regard to alternative treatment modalities, namely radical prostatectomy, high-intensity focused ultrasound, or cryotherapy.

Conflict of Interest Disclosures

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