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Scientific Article

Prognostic Score in Radiotherapy Practice for Palliative Treatments (PROPHET) Study for Bone Metastases: An Investigation Into the Clinical Effect on Treatment Prescription

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Abstract

Purpose: Bone metastases frequently occur during malignant disease. Palliative radiation therapy (PRT) is a crucial part of palliative care because it can relieve pain and improve patients' quality of life. Often, a clinician's survival estimation is too optimistic. Prognostic scores (PSs) can help clinicians tailor PRT indications to avoid over- or undertreatment. Although the PS is supposed to aid radiation oncologists (ROs) in palliative-care scenarios, it is unclear what type of support, and to what extent, could impact daily clinical practice.

Methods and Materials: A national-based investigation of the prescriptive decisions on simulated clinical cases was performed in Italy. Nine clinical cases from real-world clinical practice were selected for this study. Each case description contained complete information regarding the parameters defining the prognosis class according to the PS (in particular, the Mizumoto Prognostic Score, a validated PS available in literature and already applied in some clinical trials). Each case description contained complete information regarding the parameters defining the prognosis class according to the PS. ROs were interviewed through questionnaires, each comprising the same 3 questions per clinical case, asking (1) the prescription after detailing the clinical case features but not the PS prognostic class definition; (2) whether the RO wanted to change the prescription once the PS prognostic class definition was revealed; and (3) in case of a change of the prescription, a new prescriptive option. Three RO categories were defined: dedicated to PRT (RO-d), nondedicated to PRT (RO-nd), and resident in training (IT). Interviewed ROs were distributed among different regions of the country.

Results: Conversion rates, agreements, and prescription trends were investigated. The PS determined a statistically significant 11.12% of prescription conversion among ROs. The conversion was higher for the residents and significantly higher for worse prognostic scenario subgroups, respectively. The PS improved prescriptive agreement among ROs (particularly for worse-prognostic-scenario subgroups). Moreover, PS significantly increased standard prescriptive approaches (particularly for worse-clinical-case presentations).

Conclusions: To the best of our knowledge, the PROPHET study is the first to directly evaluate the potential clinical consequences of the regular application of any PS. According to the Prophet study, a prognostic score should be integrated into the clinical practice of palliative radiation therapy for bone metastasis and training programs in radiation oncology.

Introduction

Bone metastases frequently occur during malignant disease. The incidence of bone metastases is expected to rise due to an increase in the survival times of patients with cancer.[1] Palliative radiation therapy (PRT) is a crucial part of palliative care; it can efficiently relieve pain and improve the quality of life of patients.[2,3] Such efficacy does not seem to be dependent on either the radiation therapy delivered dose or treatment length; several randomized trials have produced similar outcomes between long-course radiation therapy (30 Gy in 10 fractions) and short-course radiation therapy (8 Gy in 1 fraction or 20 Gy in 5 fractions).[4]

Often, a clinician's survival estimation is too optimistic, overestimating patient survival and thus prescribing PRT with schedules that are too long.[5] Moreover, close to 10% of patients have received PRT during the last week of life.[6]

Palliative RT is a different clinical resource with respect to medical oncology; it is palliative care's clinical therapeutic option (not only an active oncological therapy), and it can and should be administered in palliative settings whenever indicated. The assumption that, similar to chemotherapy, it should not be prescribed in the last months of survival is incorrect. PRT has been proven effective if properly prescribed, even in the last 3 months of survival.[7] PRT should also be provided to patients dealing with complex logistic scenarios, possibly limiting their chances of receiving it.[8] Even for patients presenting with COVID-19 positivity, PRT should not be denied to those presenting a clear clinical palliative indication for PRT, preferring suboptimal palliation of symptoms instead.[9]

Nevertheless, the choice of the indication for PRT and the selection of the proper treatment modality and schedule can be challenging; if not adequate, it can prevent the relief of the patients' symptoms, even providing unbalanced side effects, and cause useless time consumption under therapy.

An international consensus regarding the use of PRT suggests the wide administration of a single dose of 8-Gy regimen, particularly for clinical cases with worse prognosis. Recently, stereotactic body radiation therapy (SBRT) has been investigated for its promising results in terms of symptom palliation[10]; definitive results are still pending, and deciding whether and when to prescribe it represents an issue. Physicians often incorporate patient life-expectancy estimates into palliative cancer care.[11]

Prognostic scores (PSs) can help clinicians to tailor PRT indications to avoid overtreatment or undertreatment. Estimating prognosis is a priority, specifically for patients with a relatively short life expectancy. Several prediction models have been developed[12,13]; however, it is unclear whether 1 PS can be considered superior to another. Moreover, although the use of a PS is supposed to aid radiation oncologists (ROs) in the palliative-care scenario, it is not clear what type of support, and to what extent, could impact daily clinical practice.

We present the results of the PROPHET (Prognostic Score in radiation therapy Practice for Palliative Treatments) study. We investigated the potential clinical outcomes of applying a validated PS through a national-based simulation of PRT prescriptions in clinical cases derived from real clinical practice. As a result, the details of the decision's influence, determined by the introduction of a PS in the treatment-prescription process, have been deepened. The main aim of this study was not to investigate whether a PS is superior to any other, whether the selected PS in itself can be of aid for ROs, or whether the selected PS can appropriately define the survival expectation. We focused on the chance that introducing a tool of survival prognostication would affect the clinical decision for PRT.

Materials and Methods

Overview

We performed a national-based investigation of ROs' prescriptive decisions on simulated clinical cases within the network of Italy's national radiation oncology society (Associazione Italiana di Radioterapia ed Oncologia Clinica [AIRO] - Italian Association of Radiation Clinical Oncology). ROs registered in AIRO were interviewed about PRT prescriptions with regard to different simulated clinical case presentations (before and after revealing to them the associate prognostic class for each case). Each RO was interviewed for all the simulated clinical cases.

Nine clinical cases from real-world clinical practice were selected for this study. Cases were selected to represent different clinical scenarios for patients affected by painful bone metastases that are potentially suitable for PRT. Clinical cases were selected to belong to different and globally balanced prognostic classes (ie, good, intermediate, and worse) according to stratification through a validated PS available in the literature.

We referred to the Mizumoto Prognostic Score (MPS),[14] a validated prognostic score available in the literature and already clinically applied in some trials for bone metastases.[15-17] Each case description contained complete information about the parameters defining the prognosis class according to the MPS (Table 1).

Table 1 Mizumoto score parameters for prognostic class identification*

Prognostic factor	Score
Type of primary tumor	
Favorable†	0
Unfavorable	3
ECOG PS >3	3
Visceral metastases	2
Previous chemotherapy	2
Hypercalcemia	2
Multiple bone metastases	1
Elderly (>71 y)	1

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group performance status.
* Class A: score 0-4; class B: score 5-9; class C: score 10-14.
† Breast, prostate, and thyroid cancers (except anaplastic cancer) and lymphoma.
Adapted from Mizumoto et al.[14]

A questionnaire was prepared for each clinical case, which included a group of 3 questions that (1) asked the RO to provide a prescription after detailing the clinical case feature but not the MPS prognostic class definition; (2) asked if the RO wanted to change the prescription once the MPS prognostic class definition was revealed; and (3) in case of a change of the prescription, asked for a new prescriptive option. Within each questionnaire, for each clinical case, the same 4 PRT prescriptive options were available ("30 Gy in 10 fractions," "20 Gy in 5 fractions," "8 Gy in 1 fraction," or "other—please specify"). An example of a questionnaire reporting a clinical case is available in Fig 1. To ensure homogeneity in the way questionnaires were interpreted among participants and how they accordingly answered, the questionnaires were not completed by participants themselves; an interview was performed to propose the questionnaire, ensuring the same interpretation of questions, options, and prognostic score interpretation by participants. Of note, the MPS shuffles into 3 prognostic classes: "worse," "intermediate," and "good" prognosis. The interviewed ROs were asked to just refer to this classification without providing deeper details about the expected months of estimated survival (eg, the "worse" prognosis profile, instead of "6 months of residual life expected").

Experienced ROs who were not residents or ROs dedicated to PRT were selected to perform interviews. The ROs who performed interviews were all trained for this purpose by the same RO (the supervisor of the project) to ensure proper interpretation of the questionnaire by each participant. The ROs administering questionnaires through interviews had no influence on the answers; they were required to strictly report the participant's answer.

Clinical Case 1

69-yr-old male Pz with prostate neoplasm diagnosed in 2011 (cT1c cN0; Gleason 4+4), treated with Radiotherapy and Hormone Therapy.

From June 2017 linear PSA rise to 12 ng/mL in February 2018; hematochemical examinations also found hypercalcemia. In March 2018, the patient went to the PS for acute low back pain for which the patient was taking upright position with difficulty (ECOG 3). CT TB with MDC and subsequent MRI of the spine found the presence of a secondary lesion at the level of L1. Two additional small centimeter areas of bone involvement were present in the pelvis at the level of the SN iliac wing and DX ischio-pubic branch. Only painful site in L1 (NRS 7). The orthopedist ruled out stabilization surgery

QUESTION 1.

What type of prescription would you use for this patient?

a) 30 Gy/3 Gy fr on symptomatic site

b) 20 Gy/4 Gy fr on symptomatic site

c) 8 Gy/8 Gy fr on symptomatic site

(d) other (_____) [If respondent opts for SBRT: ask for fractionation, dose, reference isodose, and whether alternate or consecutive day therapy]

QUESTION 2.

According to the Mizumoto Prognostic Score, the patient falls into class B: prognosis between 6 and 12 months (6/14 points for: hypercalcemia; multiple bone metastases; ECOG 3).

In light of the current data would you change the prescription?

a) yes

b) no

QUESTION 3.

If "yes" to QUESTION 2, the fractionation you would choose would be:

a) 30 Gy/3 Gy fr on symptomatic site

b) 20 Gy/4 Gy fr on symptomatic site

c) 8 Gy/8 Gy fr on symptomatic site

d) other (_____)[If respondent opts for SBRT: ask for fractionation, dose, reference isodose, and whether alternate or consecutive day therapy]

Figure 1 Example of a questionnaire reporting a clinical case.

The ROs selected for administration of interviews had no specific relationship with the participants that could possibly influence the selection of a certain answer over any other.

Each questionnaire (including each simulated case) was proposed to ROs with different levels of expertise (see details in Study Population). The prescriptions of the ROs, changes in prescription, agreement between the different operators interviewed (clustered by expertise level), and specific prescriptive correspondences to literature standards were analyzed globally and by subgroups.

At each interview, the questionnaire was completed by the interviewer upon indications of the participant. The data were then reported into a predesigned Microsoft Excel file.

Clinical case description

All patients were referred to clinical presentations suitable for palliative and antalgic radiation therapy with at least 1 symptomatic site. All cases contained complete anamnestic information, including the numerical-rating-scale pain value and the data required to compile the MPS. Three cases referred to patients who had the most favorable prognosis (MPS class A [MizA]), 3 had intermediate prognoses (MPS class B [MizB]), and 3 had unfavorable prognoses (MPS class C [MizC]) according to MPS stratification.

Prescriptive options

There were 4 prescriptive proposals for each of the 9 simulated cases: (1) 30 Gy (3 Gy per 10 fractions), (2) 20 Gy (4 Gy per 5 fractions), (3) 8 Gy in a single fraction, or (4) other. Interviewed ROs were asked to specify the treatment option whenever the option "other" was chosen; moreover, if the answer was "SBRT," ROs were requested to detail the total dose, fraction dose, isodose prescription, and schedule (treatment every day or every other day). Answer 1 was classified as good clinical practice, and answers 2 and 3 were classified as the gold standard.

Questionnaires

Nine questionnaires were prepared for each clinical case. Each of these included 3 questions: the first asked for a prescription proposal without specifying the prognostic class, the second asked for a possible modification of the prescription after disclosure of the prognostic data, and the third confirmed or varied the previous prescription.

Study population

Clinical cases were presented to ROs registered with AIRO. The ROs were classified according to years of clinical experience (senior if at least 8 years or junior if less than 8 years) and clinical focus ("dedicated" if clinical and/or scientific activity was dedicated to PRT and "non-dedicated" if not). The third category was the residents. Three RO categories were defined: dedicated to PRT (RO-d), nondedicated to PRT (RO-nd), and resident in training (IT). Interviewed ROs were distributed along different regions of the country.

Analysis description

Conversion rate

The rate at which the ROs preferred to change their initial prescription after acquiring the prognostic stratification results by the MPS was assessed. We performed the conversion-rate analysis by first referring to the overall conversion rate (analyzing the answers on the 9 clinical cases together) and then performing a subgroup analysis for the different prognostic subgroup cases (grouping together the 3 clinical cases classified as MizA, the 3 classified as MizB, and the 3 classified as MizC) and by the RO's expertise type (ie, RO-d, RO-nd, and IT). We analyzed the mean and median conversion rates. After

applying a test on the normal distribution of the sample to justify the use of the Kruskal-Wallis test, we performed the Kruskal-Wallis test to investigate the statistical significance of changes in conversion rates.

Agreement

The prescriptive agreement among ROs was assessed. We applied the Fleiss κ test to analyze the agreement rate and κ value of the agreement between the various operators.[18] According to the Fleiss κ test, the agreement was assessed as poor if the κ value was <0.4, intermediate to good if the κ value ranged between 0.4 and 0.75, and excellent if the κ value was >1.05. The agreement was first globally analyzed for all the ROs interviewed (overall agreement).

Subgroup analysis was performed for the different prognostic subgroup cases (grouping together the 3 clinical cases with MizA, the 3 clinical cases with MizB, and the 3 clinical cases with MizC). Subgroup analysis was performed for the different expertise subgroups (RO-d, RO-nd, and IT).

Both global and subgroup analyses evaluated the variation of the agreement in terms of the percentage of prescriptive variation and κ values. The mean, modal, and standard deviation (SD) were analyzed.

Prescriptive trend

In this single-blind (for interviews only) study, a predefinition of the expected proper association between the clinical case's prognostic class and prescriptive answer option was set. The prescriptive answer options (ie, "8 Gy in 1 fraction," "20 Gy in 5 fractions," or "30 Gy in 10 fractions") were labeled as *gold standard, good clinical practice*, and *other*, respectively.

The available answer options for each clinical case were classified according to relative PS stratification. In particular, answers for the 3 worse-prognosis clinical cases (ie, MizC) were defined as *gold standard* for the answer "8 Gy in 1 fraction" and *good clinical practice* for the answers "20 Gy in 5 fractions" or "30 Gy in 10 fractions." Answers for the 3 intermediate-prognosis clinical cases (ie, MizB) were defined as *gold standard* for the answers "8 Gy in 1 fraction" or "20 Gy in 5 fractions" and as *good clinical practice* for the answer "30 Gy in 10 fractions." The tendency to prescribe solutions considered the gold standard or good clinical practice was assessed.

We analyzed the percentage of answers with a proper correspondence between prescriptive answer options and the expected proper association, both before and after the revelation of the MPS prognostic class. Statistical analysis of the variation was performed using the Pearson χ^2 test. An evaluation of the answer distribution was performed only for the 3 good-prognosis clinical cases (ie, MizA).

Overview of the answer "other"

The details of the answer "other" for prescriptions were evaluated. The clustering of alternative prescriptions concerning the 3 prognostic subgroup classes according to MPS (ie, MizA, MizB, and MizC) was distributed.

In addition, the prescriptive details for ROs' answers referring to SBRT (as an alternative to the default proposed options) are detailed in terms of the total dose, dose per fraction, isodose prescription, and daily schedule. The main SBRT prescription grouping included total dose and fractionation. Detailed SBRT prescription grouping included the total dose, fractionation, isodose prescription, and daily scheduling.

Results

Between June and December 2019, 206 ROs were interviewed. Among the 206 ROs, the subgroup classification according to expertise levels was 68 RO-d, 88 RO-nd, and 50 IT. Results are reported for conversion rates, agreement, and prescriptive trend.

Conversion rate (after MPS information)

Overall conversion rate

Among the whole group of 206 ROs (RO-d, RO-nd, and IT), the rate of prescriptive modification after the acquisition of the MPS information for all 9 cases was analyzed. The median conversion rate was 11.12% (mean, 13.9%; SD, 10.54%; range, 7.8%-21%; $P < .004$).

Conversion rate subgroup analysis by expertise level

The median conversion rate for RO-d was 11.11% (mean, 13.0719%; SD, 15.47017%; range, 0%-55.56%); for RO-nd, it was 11.11% (mean, 10.6061%; SD, 11.41464%: range, 0%-44.44%); and for IT, it was 22.22% (mean, 20.8889%; SD, 18.18690%; range, 0%-66.67%).

Conversion rate subgroup analysis by prognostic class

The rate of prescriptive modification after the acquisition of MPS information for the 9 cases, stratified by the 3 triplets of prognostic class (ie, 3 MizA cases, 3 MizB cases, and 3 MizC cases), was assessed. The percentage of conversion rates for MizA cases was 3.442% ($P < .179$); for MizB cases, it was 4.219% ($P < .12$); and for MizC cases, it was 13.649% ($P < .001$).

Agreement before and after MPS information

Overall RO agreement

An analysis of the overall agreement for all 9 contemporary cases evaluated among all 206 RO prescriptions, both before and after the acquisition of the MPS information, was performed. Overall RO agreement before and after the acquisition of the MPS information was 38.34% (free-marginal κ, 0.18; 95% confidence interval [CI], 0.09-0.26) and 43.18% (free-marginal κ, 0.24; 95% CI, 0.13-0.36), respectively, with an absolute agreement variation of 4.84%. The agreement remained within the "poor" class.

Agreement subgroup analysis by expertise level

A subgroup investigation analyzed the agreement for all 9 cases among the 68 ROs dedicated to PRT (overall RO-d agreement) both before and after the acquisition of the MPS. Overall RO-d agreement before and after the acquisition of the MPS was 39.86% (free-marginal κ, 0.20; 95% CI, 0.10-0.30) and 44.81% (free-marginal κ, 0.26; 95% CI, 0.13-0.40), respectively, with an absolute agreement variation of 4.95%. The agreement remained within the "poor" class.

We analyzed the agreement for all 9 cases among the 88 ROs not dedicated to PRT (overall RO-nd agreement) both before and after the acquisition of the MPS. Overall RO-nd agreement before and after the acquisition of the MPS was 37.65% (free-marginal κ, 0.17; 95% CI, 0.08-0.26) and 41.47% (free-marginal κ, 0.22; 95% CI, 0.11-0.33), respectively, with an absolute agreement variation of 3.82%. The agreement remained within the "poor" class.

We analyzed the agreement for all 9 contemporary cases among the 50 IT ROs (overall IT agreement) both before and after the acquisition of the MPS. Overall IT agreement before and after the acquisition of the MPS was 38.23% (free-marginal κ, 0.18; 95% CI, 0.10-0.25) and 44.93% (free-marginal κ, 0.27; 95% CI, 0.15-0.38), respectively, with an absolute agreement variation of 6.70%. The agreement remained within the "poor" class.

In brief, the agreement rate was improved in all the subgroup categories (RO-d, RO-nd, and IT) with a range of 3.82% to 6.70%; The agreement remained within the "poor" class after the acquisition of the MPS information.

Agreement subgroup analysis by prognostic classes

We analyzed the agreement by the subgroups of the prognostic classes belonging to the triplets of cases, MizA, MizB, and MizC, before and after acquiring the MPS information.

Agreement for the 3 MizA clinical cases before and after the acquisition of the MPS information was 31.92% (free-marginal κ, 0.09; 95% CI, 0.02-0.16) and 33.56% (free-marginal κ, 0.11; 95% CI, 0.04-0.18), respectively, with an absolute agreement variation of 1.64%. The agreement remained within the "poor" class.

Agreement for the 3 MizB clinical cases before and after the acquisition of the MPS was 32.94% (free-marginal κ, 0.11; 95% CI, 0.06-0.15) and 36.33% (free-marginal κ, 0.15; 95% CI, 0.10-0.21), respectively, with an absolute agreement variation of 3.39%. The agreement remained within the "poor" class.

Agreement for the 3 MizC clinical cases before and after the acquisition of the MPS was 50.17% (free-marginal κ, 0.34; 95% CI, 0.24-0.43) and 59.66% (free-marginal κ, 0.46; 95% CI, 0.33-0.59), respectively, with an absolute agreement variation of 9.49%. The agreement class changed from "poor" to "intermediate."

Notably, based on the CI reported for agreement before and after the acquisition of the MPS, none of the previously reported improvements in the agreement were statistically significant.

Based on the stratification of free-marginal κ values into "poor," "intermediate-good," and "excellent" agreement, only the agreement on MizC cases revealed a shift of class (from "poor" to "intermediate-good").

Prescriptive trend

Gold standard (8 Gy in 1 fraction) for MizC cases (worse prognosis) before and after MPS information

Among the whole group of 206 ROs (RO-d, RO-nd, and IT), the prescriptive trend to select the option "8 Gy in 1 fraction" for the 3 cases with the worst prognosis (MizC) was evaluated. It was 63.6% and 74.4% before and after the acquisition of the MPS information, respectively ($P < .0001$).

The median percentage of ROs choosing the 8-Gy prescription was analyzed by expertise-level subgroups. For RO-d, it was 68.6% and 78.4% before and after MPS information, respectively ($P = .025$). For RO-nd, it was 64.0% before and 71.2% after MPS information, respectively ($P = .077$). For IT, it was 56.0% before and 74.7% after MPS information, respectively ($P < .0001$).

Gold standard (8 Gy in 1 fraction or 20 Gy in 5 fractions) for MizB cases (intermediate prognosis) before and after MPS information

Among the whole group of 206 ROs (RO-d, RO-nd, and IT), the prescriptive trend to select the option "8 Gy in 1 fraction" or "20 Gy in 5 fractions" for the 3 cases at intermediate prognosis (MizB) was evaluated. It was 68.4% and 78.4 % before and after the acquisition of the MPS information, respectively ($P < .0001$).

MizA cases (good prognosis) before and after MPS information

We analyzed, among the 206 ROs (RO-d, RO-nd, and IT), the rate and distribution of prescriptive modification

Table 2 Prescriptive trend for Mizumoto A cases (ie, "good prognosis")

Prescription answer	Responses, n/total n (%)*	
	Pre-MPS	Post-MPS
A: 30 Gy, 3 Gy per 10 fx	259/539 (41.9)	280/53 (45.3)
B: 20 Gy, 4 Gy per 5 fx	179/346 (29.0)	167/346 (27.0)
C: 8 Gy in 1 fx	50/85 (8.1)	35/85 (5.7)
D: Other	130/266 (21)	136/266 (22.0)

Abbreviations: fx = radiation therapy fraction; MPS = Mizumoto Prognostic Score.
* $P = .260$.

before and after the acquisition of the MPS for the 3 MizA cases. For this subgroup, no clustering for the prescriptive trend was performed. The results are reported in Table 2.

Overview of answer "other"

An overview of the details provided for answers of the option "other" among the whole group of 206 ROs, for all 9 cases, both before and after MPS information, is reported in Table 3. The answers associated with selecting "other prescription," grouped by clinical-case prognostic classes, are shown in Table 4.

The details of prescriptions referring to SBRT among answers of "other" have been grouped in Supplementary Material 1. The details of the SBRT prescriptions, including all specific differences, are described in Supplementary Material 2. Notably, the study was performed on 2019, before the publication of many relevant evidences addressing the indication for prescription of SBRT for bone metastases.

Discussion

The present PROPHET study reports the findings of a national-based investigation of the clinical effects of using a PS on prescriptive approaches by ROs. Clinicians were asked to provide their preferred prescription for PRT in 9 clinical cases. In each case, all clinical information detailing the prognostic profiling according to the MPS[14] was available to the clinicians. Once the clinician defined the prescription for each of the 9 cases, the result of the prognostic classification according to the MPS was revealed (ie, best, intermediate, or worse prognosis). Clinicians were then free to exchange the indicated prescription for another available option. Among the 206 ROs interviewed, the PROPHET study found that a significant rate (11.12%) of the overall prescriptions were converted into a different one once the associated prognostic class was revealed. These data were, in particular, significantly and more widely represented for the worse prognostic

Table 3 Details and distribution of answers associated with selecting option D: "Other prescription"

	Answers, n*									
	Case 1, Miz B	Case 2, Miz A	Case3, Miz C	Case 4, Miz A	Case 5, Miz B	Case 6, Miz A	Case 7, Miz B	Case 8, Miz C	Case 9, Miz C	All cases
SBRT	17	36	0	24	3	53	16	8	4	161
RT, non-SBRT asymptomatic	1	1	0	0	0	8	0	0	0	10
RT, non-SBRT symptomatic	3	7	1	4	2	0	0	1	0	18
Half body	0	0	1	0	0	0	0	0	0	1
8-Gy repeatable	0	0	2	0	1	0	0	3	1	7
I 131	0	0	0	0	2	0	0	0	0	2
No RT indication	1	0	0	0	0	0	0	0	0	1
Total answers pre-MPS	22	44	4	28	8	61	16	12	5	200
Answers of "SBRT" pre-MPS, %	77.27	88.81	0	85.71	37.50	86.88	100	66.67	80	80.5
Total answers post-MPS	22	50	5	30	8	63	17	13	6	214
Answers of "SBRT" post-MPS, %	77.27	84	0	86.66	37.50	90.16	94.11	61.53	66.67	79.90

Abbreviations: I 131 = metabolic radiation therapy with iodine 131; MPS = Mizumoto Prognostic Score; RT = radiation therapy; SBRT = stereotactic body radiation therapy.
* MPS class A (MizA) had the most favorable prognoses, MPS class B (MizB) had intermediate prognoses, and MPS class C (MizC) had unfavorable prognoses.

Table 4 Answers associated with selection of option D: "Other prescription," grouped by clinical case prognostic classes

	Answers by prognostic class, n*		
	MizA	MizB	MizC
SBRT	120	36	28
RT non-SBRT asymptomatic	9	1	0
RT non-SBRT symptomatic	11	6	3
Half body	0	0	1
8-Gy repeatable	0	1	6
I 131	0	2	0
No RT indication	0	1	0

Abbreviations: I 131 = metabolic radiation therapy with iodine 131; RT = radiation therapy; SBRT = stereotactic body radiation therapy.
* MPS class A (MizA) had the most favorable prognoses, MPS class B (MizB) had intermediate prognoses, and MPS class C (MizC) had unfavorable prognoses.

presentations (ie, Mizumoto class C) and among ITs (ie, residents). The PRT prescriptions after the introduction of categorization by a PS increased the ROs' overall agreement, never introducing inhomogeneity of choice among clinicians owing to the introduction of a PS. The PS determined a more relevant agreement improvement for the clinical cases in the worst prognostic class (MizC presentations); the agreement improvement was slightly more relevant among the IT subgroups. Finally, after introducing the PS, a statistically significant shift toward the standard prescription clusters (eg, 8 Gy in a single fraction for cases with worse prognosis) was reported. For many years, the scientific literature dedicated to using a PS, particularly in PRT, claimed the importance of such a tool to support clinical prescriptive choices. Specifically, the main underlying issues are represented by the fact that clinicians facing palliative settings for radiation therapy tend to overestimate survival, prescribe excessively long treatment schedules, avoid referring to the standard approaches, and prescribe PRT during a patient's last days of life.[19-21] On the other hand, not prescribing PRT is also a mistake: it is a fundamental part of palliative care and should be adopted to provide relief to patients at any time. In contrast to active systemic treatment (eg, chemotherapy), the activation of palliative care for the end of a patient's life should not avoid the administration of radiation therapy, even for patients in complex logistic scenarios or cases of COVID-19 positivity.[8,9] When appropriately applied, PRT can even improve patients' performance status[22] and increase their quality of life[23,24] (the ultimate goal of palliative care), even if administered within the last 3 months.[7] The issue is properly defining the indication for PRT and the most appropriate schedule. Many models of PS are currently available in the literature, potentially supporting clinicians' decisions. Some are built on series not strictly including radiation therapy but are useful to outline the expected survival from a palliative perspective[25]; some are built on series including PRT of any type,[26] others mainly refer to models determined by case series that have administered PRT to spinal metastases,[27] and there is evidence referring to series dedicated to SBRT for bone metastases.[28] It is neither clear nor investigated whether one model is technically superior to another: a wise approach could be to select an easy model to calculate, based on an adequate patient number. In recent years, SBRT has been advocated as more efficient than standard PRT to relieve metastatic bone pain[10]; however, evidence in this regard is inconclusive, and although promising and sometimes adopted outside clinical trials, this option is still under investigation. From a clinical-trial-setting perspective, the possibility of stratifying a group of patients into different prognostic subgroups facilitates research programs.

Despite the importance of PS, none of the main available randomized trials investigating SBRT for painful bone metastases has adopted a PS.[10,29-31] Only the phase 2 DOSIS trial published by Guckenberger et al[17] formally applied MPS to stratify patient selection; the same PS was adopted in a randomized phase 3 trial currently recruiting patients (PREST trial).[16]

The PROPHET study selected MPS[14] for similarity to the last two previously mentioned trials. To the best of our knowledge, the PROPHET study is the first to directly evaluate the potential clinical consequences of the regular application of a PS, irrespective of the application (the MPS or another). Although many reports state that 8-Gy single-fraction PRT should be preferred, namely for the worst prognostic scenarios,[32] underuse of such an approach is still reported.[33-35] Reasons for such underuse could be ascribed to multiple factors, including culture, spreading knowledge about a single fraction, and even reimbursement.

In our study, using the PS seemed to facilitate the selection of a standard approach, increase the conversion of prescriptions for the worst presentations, and improve agreement, particularly among less-experienced ROs, thus determining a positive cultural effect. Although the worst prognostic presentation should be easiest to evaluate by

ROs, the previously mentioned factors can prevent or limit the identification of the relative prognostic class. Using a PS can facilitate an adequate assessment, improve agreement among clinicians, and facilitate the application of standard approaches.

Our study has some limitations. It was not based on clinical prescriptions in real practice, although each clinical case was retrieved from real clinical cases. However, interviewing such a large number of ROs resulted in this being the only option. Moreover, the study was a wide, national-based analysis, but it was restricted to a single country (through the involvement of AIRO). Future perspectives include extending such an approach to representatives from different countries.

Conclusion

According to the PROPHET study, a prognostic score should be integrated into the clinical practice of palliative radiation therapy for bone metastasis.

The positive effects of the prognostic score on clinical practice included the improvement of agreement among clinicians and a significant increase in standard-approach prescriptions, particularly for the worst clinical case presentations (significantly more often referred to a single-dose palliative treatment). Moreover, it can improve the training of residents. It was determined that a statistically significant conversion of 11.12% of the prescriptions was assessed ahead of the availability of information derived by such a decision-support tool.

Finally, this simple and not-time-consuming tool can improve prognostic stratification, which might enhance the homogeneity of enrollment into clinical trials and facilitate the evaluation of results to draw conclusions.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101134.

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