Prognostic score in RadiOtherapy PracticE for palliative Treatments (PROPhET study) for bone metastases: an investigation into the clinical impact on treatment prescription.

Cellini Francesco MD, Di Rito Alessia MD, Siepe Giambattista MD, Pastore Francesco MD, Lattanzi Elisabetta MD, Meaglia Ilaria MD, Tozzi Angelo MD, Manfrida Stefania MD, Longo Silvia MD, Saldi Simonetta MD, Cassese Raffaele MD, Arcidiacono Fabio MD, Fiore Michele Prof, Masiello Valeria MD, Mazzarella Ciro MD, Diroma Antonio MD, Miccichè Francesco MD, Maurizi Francesca MD, Dominici Luca MD, Scorsetti Marta Prof, Santarelli Mario MD, Fusco Vincenzo MD, Aristei Cinþha Prof, Deodato Francesco Prof, Maria Antonietta Gambacorta Prof, Maranzano Ernesto Prof, Muto Paolo MD, Vincenzo Valentini Prof, Alessio Giuseppe Morganti Prof, Marino Lorena MD, Costanza Donati MD, Rossella Di Franco MD

PII: S2452-1094(22)00240-8
DOI: https://doi.org/10.1016/j.adro.2022.101134
Reference: ADRO 101134

To appear in: Advances in Radiation Oncology

Received date: 14 October 2022
Accepted date: 18 November 2022

Please cite this article as: Cellini Francesco MD, Di Rito Alessia MD, Siepe Giambattista MD, Pastore Francesco MD, Lattanzi Elisabetta MD, Meaglia Ilaria MD, Tozzi Angelo MD, Manfrida Stefania MD, Longo Silvia MD, Saldi Simonetta MD, Cassese Raffaele MD, Arcidiacono Fabio MD, Fiore Michele Prof, Masiello Valeria MD, Mazzarella Ciro MD, Diroma Antonio MD, Miccichè Francesco MD, Maurizi Francesca MD, Dominici Luca MD, Scorsetti Marta Prof, Santarelli Mario MD, Fusco Vincenzo MD, Aristei Cinþha Prof, Deodato Francesco Prof, Maria Antonietta Gambacorta Prof, Maranzano Ernesto Prof, Muto Paolo MD, Vincenzo Valentini Prof, Alessio Giuseppe Morganti Prof, Marino Lorena MD, Costanza Donati MD, Rossella Di Franco MD, Prognostic score in RadiOtherapy PracticE for palliative Treatments (PROPhET study) for bone metastases: an investigation into the clinical impact on treatment prescription, Advances in Radiation Oncology (2022), doi: https://doi.org/10.1016/j.adro.2022.101134

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that,
during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
TITLE:
Prognostic score in RadiOtherapy PracticE for palliative Treatments (PROPhET study) for bone metastases:
an investigation into the clinical impact on treatment prescription.

Running Title: Prognostic score in Radiotherapy

Authors: Cellini Francesco MD1,2*, Di Rito Alessia MD3, Siepe Giambattista MD4, Pastore Francesco MD5, Lattanzi Elisabetta MD6, Meaglia Ilaria MD7, Tozzi Angelo MD7, Manfrida Stefania MD2, Longo Silvia MD5, Saldi Simonetta MD8, Cassese Raffaele MD9, Arcidiacono Fabio MD10, Fiore Michelle Prof11, Masiello Valeria MD2, Mazzarella Ciro MD2, Diroma Antonio MD1, Micciche Francesco MD2, Maurizi Francesca MD12, Dominici Luca MD13, Scorretti Marta Prof14, Santarelli Mario MD15, Fusco Vincenzo MD16, Aristei Cinthia Prof17, Deodato Francesco Prof18, Maria Antonietta Gambacorta Prof1,2, Maranzano Ernesto Prof19,20, Muto Paolo MD21, Vincenzo Valentini Prof1,2, Alessio Giuseppe Morganti Prof4,22, Marino Lorenzo MD23, Costanza Donati MD8,24, Rossella Di Franco MD21

[Author Institutions]
1: Università Cattolica del Sacro Cuore, Dipartimento Universitario Diagnostica per immagini., Radioterapia Oncologica ed Ematologia, Roma, Italy
2: Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Roma, Italia
3: Radiotherapy Oncology Department, IRCCS "Giovanni Paolo II", Bari, Italy.
4: Radiation Oncology, IRCCS Azienda Ospedaliero Universitaria di Bologna, 40138 Bologna, Italy.
5: Radiation Oncology, Fondazione Muto Onlus - Eemicenter - Naples, Italy.
6: Radiation Oncology Unit, University Hospital of Parma, Parma, Italy
7: Istituti Clinici Scientifici Maugeri IRCCS, 27100 Pavia, Italy.
8: Section of Radiation Oncology, Perugia General Hospital, Perugia, Italy. Electronic address: simonetta.saldi@ospedale.perugia.it
9: Radiotherapy Unit, Ospedale San Camillo de Lellis, Rieti, Italy.
10: Radiation Oncology, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy
11: Radiation Oncology, Campus Bio-Medico University, Rome, Italy.
12: Radiation Oncology, A.O. Ospedali Riuniti Marche Nord, Pesaro, Italy.
13: Department of Radiotherapy, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089, Rozzano, Milan, Italy.
14: Department of Radiotherapy, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089, Rozzano, Milan, Italy; Humanitas University, Department of Biomedical Sciences, Via Rita Levi Montalcini 4, 20090 Pieve Emanuele, Milan, Italy.
15: Radiotherapy Unit, Ospedale San Camillo de Lellis, Rieti, Italy.
16: Radiotherapy Oncology Department, IRCCS CROB, Rionero In Vulture, Italy
17: Radiation Oncology, Department of Surgical and Biomedical Science, University of Perugia and Perugia General Hospital, Perugia, Italy.
18: Radiotherapy Unit, Gemelli Molise Hospital, Campobasso, Italy
19: Radiotherapy Oncology Centre, Santa Maria Hospital, Terni, Italy.
Abstract
Background: Bone metastases (BM) frequently occur during malignant disease. Palliative radiotherapy (PRT) is a crucial part of palliative care, as it can relieve pain and improve patients' quality of life. Often, a clinician’s survival estimation is too optimistic. Prognostic scores (PS) can help clinicians tailor PRT indications to avoid over- or under-treatment. Although PS is supposed to aid radiation oncologists (RO) in palliative care scenarios, it is unclear what type of support and the extent to which it could impact daily clinical practice.

Materials and Methods: We performed a national-based investigation of the prescriptive decisions on simulated clinical cases. 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 (we selected 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 composed by the same three questions per each clinical case, asking: i) the prescription after detailing the clinical case feature but not the PS prognostic class definition; ii) if RO wanted to change the prescription once the PS prognostic class definition was revealed; and iii) in case of change of the
prescription, a new prescriptive option. Three RO categories were defined: dedicated to PRT (RO-d), non-dedicated to PRT (RO-nd), and resident in training (IT). Interviewed ROs were distributed along 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 resident and significantly higher for worse prognostic scenario subgroups, respectively. 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).

Conclusion: According to the Prophet study, a prognostic score should be integrated into the clinical practice of palliative radiotherapy for bone metastasis and training programs in radiation oncology.

BACKGROUND:

Bone metastases (BM) frequently occur during malignant disease. The incidence of BM is expected to rise over the years due to an increase in the survival times of patients with cancer [1]. Palliative radiotherapy (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 radiotherapy delivered dose or treatment length; several randomized trials have produced similar outcomes between long-course radiotherapy (30 Gy in 10 fractions) and short-course radiotherapy (8 Gy in 1 fraction, 20 Gy in 5 fractions) [4].

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

PRT 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 three 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 coronavirus disease 2019 (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 patients’ symptoms, even providing unbalanced side effects and 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 radiotherapy (SBRT) has been investigated for its promising results in terms of symptom palliation [10]; definitive results are still pending and deciding whether and when prescribing represents an issue. Physicians often incorporate patient life expectancy estimates into palliative cancer care [11].

Prognostic scores (PS) can help clinicians to tailor PRT indications in order to avoid over- or under-treatment. Estimating prognosis is a priority, specifically for patients with a relatively short life expectancy. Several prediction models have been developed [12] [13].

It is unclear whether one PS can be considered superior to the other. Moreover, although the use of 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 it could impact daily clinical practice.
We present the results of the PROPhET (Prognostic score in RadiOtherapy PracticE for palliative Treatments). We investigated the potential clinical impact 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 PS in the treatment prescription process, have been deepened. The main aim of this study is neither to investigate if one PS is superior to nay other, nor if the selected PS in itself can be of aid for ROs, nor if the selected PS can appropriately defin the survival expectation. We focus on the chance that introducing a tool of survival prognostication can affect the clinical decision for PRT.

MATERIALS AND METHODS:

Overview

We performed a national-based investigation of RO’s prescriptive decisions on simulated clinical cases within the network of the Italian Radiation Oncological National Society (Associazione Italiana di Radioterapia ed Oncologia Clinica; Italian Association of Radiation Clinical Oncology -AIRO-). ROs registered in the AIRO association 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 BM that are potentially suitable for PRT. Clinical cases were selected to belong to different and globally balanced prognostic classes (i.e., good, intermediate, and worse) according to stratification through a validated PS available in the literature.

We referred to the Mizumoto Prognostic Score (MPS) [14], since it is a validated prognostic score available in literature and already clinically applied in some trials for bone metastases [15] [16] [17]. Each case description contained complete information about the parameters defining the prognosis class according to the MPS (Table 1).

A questionnaire was prepared for each clinical case, which included a group of three questions that asked: i) the RO to provide a prescription after detailing the clinical case feature but not the MPS prognostic class definition; ii) if RO wanted to change the prescription once the MPS prognostic class definition was revealed; and iii) in case of change of the prescription, a new prescriptive option. Within each questionnaire, for each clinical case, the same 4 PRT prescriptive options were available (i.e., “30 Gy in 10 Fractions”; “20 Gy in 5 Fractions”; “8 Gy in 1 Fraction”; “Other - Please specify”). An example of a questionnaire reporting a clinical case is available in Figure 1. To ensure homogeneity of the way to interpret questionnaires among participants and to accordingly answer, the questionnaires were not fulfilled 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, MPS shuffles into 3 prognostic classes defining “worse”, “intermediate” and “good prognosis: the interviewed ROs were asked to just refer to this classification without deepen details on the expected months of estimated survival (e.g.: the “worse” prognosis profile instead to “six month of residual life expectation”).

Experienced RO (not resident, nor RO dedicated to PRT) were selected to perform interviews. The RO who performed interviews have been all trained for such purpose by the same RO (i.e.: supervisor of the project) to ensure proper interpretation of the questionnaire by each participant. The ROs administering questionnaires through interview had no influence on the answers; they have been required to strictly report the participant’s answer. The ROs selected for administration of interviewers, had no specific relationship with the participants that have possibly influenced the selection of certain answer over any other.

Each questionnaire (including each simulated case) was proposed to ROs with different levels of expertise (see details in the section “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 (globally and by sub-groups) analyzed.
At each interview the questionnaire was fulfilled by the interviewer upon indication of the participant; then the data were reported into a pre-designed excel file.

**Clinical case description**

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

**Prescriptive Options**

The prescriptive proposals were four for each of the nine simulated cases: a) 30 Gy (3 Gy per 10 fractions), b) 20 Gy (4 Gy per 5 fractions), c) 8 Gy in a single fraction, d) “Other.” Interviewed ROs were asked to specify the treatment option whenever the option “d) other” was chosen; moreover, in case the answer would have been “SBRT” ROs were requested to detail the total dose, fraction dose, isodose prescription, and schedule (“every day” or “every other day” treatment). Answers a) were classified as good clinical practice, b) and c) were classified as the gold standard.

**Questionnaires**

Nine questionnaires were prepared for each clinical case. Each of these included three 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 Italian Association of Radiation Clinical Oncology (AIRO). ROs were classified according to years of clinical experience (senior and junior if at least or less than eight years, respectively) and clinical focus (dedicated or non-dedicated if clinical and/or scientific activity was dedicated to PRT). The third category was the residents. Three RO categories were defined: dedicated to PRT (RO-d), non-dedicated 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 MPS was assessed. We performed the conversion rate analysis by first referring to the overall conversion rate (analyzing the answers on the nine clinical cases together): subgroup analysis for the different prognostic subgroup cases (grouping together the three clinical cases MizA; the three clinical cases MizB and the three clinical cases MizC, respectively) and by the RO’s expertise type (i.e., 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-K test to analyze the agreement rate and K-value of the agreement between the various operators [18]. According to the Fleiss-K test, the
agreement was assessed as poor if the k value <0.4; intermediate-good if the k-value ranged between 0.4 and 0.75; excellent if the k-value was >1.05. The agreement was first globally analyzed for all the RO interviewed (overall agreement).

Subgroup analysis was performed for the different prognostic subgroup cases (grouping together the three clinical cases MizA; the three clinical cases MizB, and the three clinical cases MizC, respectively). Subgroup analysis was performed for 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 k-value. The mean, modal, and standard deviation 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 (i.e., “8 Gy in 1 fraction”; “20 Gy in 5 fractions”; “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 three worse-prognosis clinical cases (i.e., MizC) were defined as “Gold standard” for the answer “8 Gy in 1 fraction,” “good clinical practice” for the answer “20 Gy in 5 fractions,” and “30 Gy in 10 fractions”. Answers for the three intermediate-prognosis clinical cases (i.e., MizB) were defined as “Gold standard” for the answer “8 Gy in 1 fraction” or “20 Gy in 5 fractions,” and “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 expected proper association, both before and after the revelation of the MPS prognostic class. Statistical analysis of the variation was performed using Pearson’s chi-square test. Only an evaluation of the answer distribution was performed for the three good-prognosis clinical cases (i.e., MizA).

Overview of answer “Other”

The details of the answers “Other” for prescriptions were evaluated. The clustering of alternative prescriptions concerning the three prognostic subgroup classes according to MPS (i.e., MizA, MizB, and MizC) was distributed.

In addition, the prescriptive details for RO’s 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 RO interviewed, 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.

1. Conversion rate (after MPS information)
   1.1. Overall Conversion Rate

   Among the whole group of 206 ROs (“RO-d”+ “RO-nd”+ “IT”), the rate of prescriptive modification after the acquisition of the MPS information for all nine cases was analyzed. The median conversion rate was 11.12% (mean, 13.9%; SD, 10.54; range, 7.8-21; p<0.004).

   1.2. Conversion Rate subgroup analysis by Expertise Level
Median conversion rate for RO-d was 11.11% (mean 13.0719; SD 15.47017; range 0-55.56); for RO-nd was 11.11% (mean 10.6061; SD 11.41464; range 0-44.44) and for IT was 22.22% (mean 20.8889; SD 18.18690; range 0-66.67).

1.3. Conversion Rate subgroup analysis by Prognostic Class
The rate of prescriptive modification after the acquisition of MPS information for the nine cases was stratified by the three triplets of prognostic class (i.e., three MizA cases, three MizB cases, and three MizC cases) was performed. The percentage of conversion rates for cases MizA was 3.442 % (p<0.179), for cases MizB was 4.219 % (p< 0.12) and for cases MizC was 13.649 % (p< 0.001), respectively.

2. Agreement (before and after MPS information)
2.1. Overall ROs agreement
The analysis of the overall agreement for all nine contemporary cases evaluated among all 206 RO prescriptions, both before and after the acquisition of the MPS information, was performed. Overall ROs agreement before and after the acquisition of the MPS information was 38.34% (free-marginal kappa=0.18; 95% CI [0.09-0.26]) and 43.18% (free-marginal kappa=0.24; 95% CI [0.13-0.36]), respectively, with an absolute agreement variation of +4.84%. The agreement remained within the “poor” class.

2.2. Agreement subgroup analysis by Expertise Level
A subgroup investigation analyzed the agreement for all 9 cases among the 68 RO 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 kappa=0.20; 95% CI [0.10-0.30]) and 44.81% (free-marginal kappa=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 nine 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 kappa =0.17; 95% CI for [0.08-0.26]) and 41.47% (free-marginal kappa=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 nine contemporary cases among the 50 IT (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 kappa=0.18; 95% CI [0.10-0.25]) and 44.93% (free-marginal kappa=0.27; 95% CI [0.15-0.38]), respectively, with an absolute agreement variation of +6.70%. The agreement remained within the “poor” class.

Briefly, the agreement rate was improved in all the subgroup categories (RO-d; RO-nd; IT) with a range of +3.82-+6.70%; The agreement remained within the “poor” class after the acquisition of the MPS information.

2.3. 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 MizA 3 clinical cases, before and after the acquisition of the MPS information, was 31.92% (free-marginal kappa =0.09; 95% CI [0.02-0.16], and 33.56% (free-marginal kappa=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 MizB 3 clinical cases before and after the acquisition of the MPS was 32.94% (free-marginal kappa=0.11; 95% CI [0.06-0.15]; 36.33% (free-marginal kappa=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 MizC 3 clinical cases, before and after the acquisition of the MPS was 50.17% (free-marginal kappa:0.34; 95% CI [0.24-0.43], and 59.66% (free-marginal kappa=0.46; 95% CI [0.33-0.59], respectively, with an absolute agreement variation of +9.49%. The agreement class changed from the “poor” to the “intermediate” class.

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 kappa values into “poor,” “intermediate-good,” and “excellent” agreement, only the agreement on MizC cases revealed a shift of class (from “poor” to “intermediate-good”).

3. Prescriptive Trend

3.1. Gold Standard (8 Gy/1 fraction) prescriptive trend for MizC cases (worse prognosis) before and after MPS information

Among the whole group of 206 ROs (“RO-d” + “RO-nd” + “IT”), the prescriptive trend to select the option “8 Gy in 1 fraction” for the three 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<0.0001).

The median percentage of “8 Gy prescription” was analyzed by expertise level subgroups: For RO-d was 68.6% and 78.4 before and after MPS information, respectively (p=0.025). The RO-nd was 64.0% before and 71.2% after MPS information, respectively (p=0.077). It was, 56.0% before and 74.7% after MPS information, respectively (p<0.0001).

3.2. Gold Standard (8 Gy/1 fraction+20Gy/5 fractions) prescriptive trend for MizB cases (intermediate prognosis) before and after MPS information

Among the whole group of 206 ROs (“RO-d” + “RO-nd” + “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<0.0001).

3.3. The prescriptive trend for MizA cases (good prognosis) before and after MPS information

We analyzed among the 206 ROs (“RO-d”+ “RO-nd”+ “IT”) the rate and distribution of prescriptive modification before and after the acquisition of the MPS for the three MizA cases.

For this subgroup, no clustering for the prescriptive trend was performed.

The results are reported in Table 2

3.4. Overview of answer “Other”

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

The details of prescription referred to an SBRT, among answers “Other,” have been grouped in Supplementary Material 1. The details of the SBRT prescriptions, including all specific differences, are described in Supplementary Material 2.

DISCUSSION:

The present Prophet study reports the outcome of a national-based investigation on the clinical impact of using 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 nine cases, the result of prognostic classification according to MPS was revealed (i.e., best, intermediate, or worse prognosis). Clinicians were then free to change the indicated prescription for another available option. On 206 interrogated ROs, the Prophet study found that a significant rate (11.12%) of the overall prescription has been 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 presentations (i.e., the Mizumoto class “C” - MizC-) and IT (i.e., residents). The PRT prescriptions after the introduction of categorization by PS increased the RO’s overall agreement, never introducing inhomogeneity of choice among clinicians due to the introduction of PS. PS determined a more relevant agreement improvement for the worst prognostic class clinical cases (MizC presentations); the agreement improvement was slightly more relevant among the IT subgroups. Finally, after introducing PS, a statistically significant shift toward the standard prescription clusters (e.g., 8 Gy in a single fraction for cases with worse prognosis) was reported. For many years, the scientific literature dedicated to using PS, particularly 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 radiotherapy tend to overestimate survival, prescribe excessively long treatment schedules, avoid referring to the standard approaches and apply PRT during the last days of life for the patients [19] [20] [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 (e.g., chemotherapy), the activation of palliative care for the end-of-life time of a patient should not avoid the administration of radiotherapy, even for patients in complex logistic scenarios or cases of covid-positivity [8] [9]. When appropriately applied, PRT can even improve the performance status of patients [22] and increase patients’ quality of life (QOL) [23] [24] (the ultimate goal of palliative care), even if administered within the last three 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 radiotherapy 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 BM [28]. It is neither clear nor investigated if one model is technically superior to the other: a wise approach could be to select an easy one to calculate, based on an adequate patient number. In recent years, SBRT has been advocated as a 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 BM has adopted a PS [10] [29] [30] [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: the PREST trial [16].

The Prophet study selected MPS [14] for similarity to the 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 PS, irrespective of the application (MPS or another). Although many reports state that the 8 Gy single fraction PRT should be the preferred one, namely for worst prognostic scenarios [32], underuse of such an approach is still reported [33] [34] [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 prescription for worst presentation, and improve the agreement, particularly among younger ROs, thus determining a positive cultural impact. 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 the PS can: facilitate an adequate assessment, improve the agreement among clinicians and facilitate the application of standard approaches.

Our study has some limitations: it is not based on clinical prescriptions in real practice, although each clinical case was retrieved from real clinical cases. However, interrogating such a large number of ROs, resulted in this being the only option. Moreover, the study is a wide, national-based analysis, but it is restricted to a single country (through the involvement of the National Society: Associazione Italiana di Radioterapia ed Oncologia Clinica–Italian Association of Radiation Clinical Oncology–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 radiotherapy for bone metastasis.

The positive impact of the prognostic score on clinical practice includes the improvement of agreement among clinicians and a significant increase in standard approach prescriptions, particularly for worst clinical case presentations (significantly more often referred to single-dose palliative treatment). Moreover, it can improve the training of residents. It 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, it can improve prognostic stratification by a simple and not time-consuming tool, which might enhance the homogeneity of enrolment into clinical trials and facilitate the evaluation of results to draw conclusions.

Table 1: Mizumoto Score parameters for prognostic class identification

<table>
<thead>
<tr>
<th>PROGNOSTIC FACTOR</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of primary tumor</td>
<td></td>
</tr>
<tr>
<td>- Favorable*</td>
<td>0</td>
</tr>
<tr>
<td>- Unfavorable</td>
<td>3</td>
</tr>
<tr>
<td>ECOG PS&gt;3</td>
<td>3</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>2</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>2</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2</td>
</tr>
<tr>
<td>Multiple bone metastases</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (&gt;71y)</td>
<td>1</td>
</tr>
</tbody>
</table>
ECOG PS indicates Eastern Cooperative Oncology Group's performance status.
*Breast, prostate, Lymphoma, and thyroid cancer (except anaplastic cancer).

Class A: score 0-4
Class B: score 5-9
Class C: score 10-14
*Modified by: Mizumoto et al.; 2008 American Cancer Society\(^{(14)}\)

### Table 2: Prescriptive trend for Mizumoto A cases (i.e.: “good prognosis”)

<table>
<thead>
<tr>
<th>Answer-prescription</th>
<th>Pre-MPS Answers n./n.tot (%)</th>
<th>Post-MPS Answers n./n.tot (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Answer “a”</td>
<td>259/539 (41.9%)</td>
<td>280/53 (45.3%)</td>
</tr>
<tr>
<td>30 Gy/3 Gy for fx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Answer “b”</td>
<td>179/346 (29.0%)</td>
<td>167/346 (27.0%)</td>
</tr>
<tr>
<td>20 Gy/4 Gy for fx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Answer “c”</td>
<td>50/85 (8.1%)</td>
<td>35/85 (5.7%)</td>
</tr>
<tr>
<td>8Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Answer “d”</td>
<td>130/266 (21%)</td>
<td>136/266 (22.0%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(p=0.260\)

(Legend: Pre-MPS: before introduction of Mizumoto Prognostic Score; Post-MPS: after introduction of Mizumoto Prognostic Score; Gy: Gray; fx: radiotherapy fractions)
Table 3. Detail and distribution of answers associated with selecting “Option d) - Other prescription.”

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
<th>Case 9</th>
<th>All cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mizumoto Class</td>
<td>Miz B</td>
<td>Miz A</td>
<td>Miz C</td>
<td>Miz A</td>
<td>Miz B</td>
<td>Miz A</td>
<td>Miz B</td>
<td>Miz C</td>
<td>Miz C</td>
<td></td>
</tr>
<tr>
<td>SBRT</td>
<td>17</td>
<td>36</td>
<td>0</td>
<td>24</td>
<td>3</td>
<td>53</td>
<td>16</td>
<td>8</td>
<td>4</td>
<td>161</td>
</tr>
<tr>
<td>RT non-SBRT</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>symptomatic</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Half body</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8 Gy Repeatable</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>I 131</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No RT indication</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Tot answers</td>
<td>22</td>
<td>44</td>
<td>4</td>
<td>28</td>
<td>8</td>
<td>61</td>
<td>16</td>
<td>12</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>“SBRT” pre-MPS</td>
<td>77.27%</td>
<td>88.81%</td>
<td>0%</td>
<td>85.71%</td>
<td>37.50%</td>
<td>86.88%</td>
<td>100%</td>
<td>66.67%</td>
<td>80%</td>
<td>80.5%</td>
</tr>
<tr>
<td>Tot answers post-</td>
<td>22</td>
<td>50</td>
<td>5</td>
<td>30</td>
<td>8</td>
<td>63</td>
<td>17</td>
<td>13</td>
<td>6</td>
<td>214</td>
</tr>
<tr>
<td>“SBRT” post-MPS</td>
<td>77.27%</td>
<td>84%</td>
<td>0%</td>
<td>86.66%</td>
<td>37.50%</td>
<td>90.16%</td>
<td>94.11%</td>
<td>61.53%</td>
<td>66.67%</td>
<td>79.90%</td>
</tr>
</tbody>
</table>

(Legend: Pre-MPS: before introduction of Mizumoto Prognostic Score; Post-MPS: after introduction of Mizumoto Prognostic Score; Gy: Gray; Miz: Mizumoto Class; SBRT: stereotactic Body Radiation Therapy)
Table 4. Answers associated with selection of “Option d) - Other prescription,” grouped by clinical cases prognostic classes

<table>
<thead>
<tr>
<th></th>
<th>Miz A</th>
<th>Miz B</th>
<th>Miz C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBRT</td>
<td>120</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>RT non-SBRT asymptomatic</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>RT non-SBRT symptomatic</td>
<td>11</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Half body</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8 Gy Repeatable</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>I 131</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>No RT indication</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

(Legend: Gy: Gray; Miz: Mizumoto Class; SBRT: stereotactic Body Radiation Therapy; I131: Metabolic Radiotherapy with Iodine 131)
FIGURES

Figure 1. Example of Cases-questionnaires reporting Clinical Case

Clinical Case 1

69-yr-old male Pz with prostate neoplasms 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; hematocochemical 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]
REFERENCES:


4. van der Linden YM, Steenland E, van Houwelingen HC, Post WJ, Oei B, Marijnen CA, Leer JW, Dutch Bone Metastasis Study G. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the dutch bone metastasis study. Radiother Oncol 2006;78:245-253.


