



An Italian survey on “palliative intent” radiotherapy

Stefano Pergolizzi^{1*}, Alberto Cacciola^{1*}, Silvana Parisi¹, Sara Lillo¹, Consuelo Tamburella¹,
Anna Santacaterina², Gianluca Ferini³, Francesco Cellini⁴, Lorena Draghini⁵, Fabio Trippa⁵,
Fabio Arcidiacono⁵, Ernesto Maranzano^{5,6}

¹Department of Biomedical and Dental Sciences, and Morphological, and Functional Images, University of Messina, Messina, Italy

²Radiation Oncology Unit, Papardo Hospital, Messina, Italy

³Radiation Oncology Unit — REM Radioterapia, Viagrande, Italy

⁴Radiation Oncology Unit, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico
Universitario “A. Gemelli” IRCCS, Rome, Italy

⁵Radiotherapy Oncology Centre, Santa Maria Hospital, Terni, Italy

⁶Department of Medicine and Surgery, University of Perugia, Perugia, Italy

*Co-first Authors

ABSTRACT

Background: The aim of this paper is to provide a comprehensive overview of the scenario on radiotherapy (RT) delivered with palliative intent in Italy.

Materials and methods: A structured online questionnaire was submitted to Italian radiation oncologists in order to explore the clinical practice in different areas of palliation, namely: bone, lung, brain, liver, and emergencies suitable to RT.

Results: 209 radiation oncologists took part in the study. Stereotactic body irradiation was found to be the preferred technique in lung and liver metastases, whereas 3D conformal RT was registered as the technique of choice for bone and brain metastases. The majority (98%) of participants stated to treat mainly radiotherapy emergencies with 3D conformal RT at doses ranging from 25 to 50 Gy. Re-irradiation is delivered by the majority of respondents, whereas post-treatment follow-up is done only by 51.4% of them.

Conclusions: This nationwide study highlights some heterogeneity among Italian radiation oncologists regarding treatment and follow-up of metastatic cancer patients.

Key words: palliative radiotherapy; cancer; supportive care; emergencies; metastases

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Introduction

Radiotherapy (RT) plays an important role in the palliative treatment of advanced cancers [1–3]. Considering the wide range of utilization in this clinical scenario, often there are differences in the therapeutic choice among radiation oncologists who treat metastatic cancer patients. The line between purely “palliative” and “cura-

tive” treatment is often not well defined with the consequence that palliative RT may include concurrent goals of symptoms relief, symptoms prevention, local tumor control, and possible cure [4, 5]. So, facing the same scenario of a patient with metastatic disease, therapeutic intent and RT prescription can be different depending on the radiation oncologist who takes care of the patient.

Address for correspondence: Sara Lillo, MD, Department of Biomedical and Dental Sciences, and Morphological, and Functional Images, University of Messina, Messina, Italy; tel: (+39) 0902212931; e-mail: lillosara3@gmail.com

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Table 1. The questionnaire used in the Italian Survey

Questionnaire — Italian survey on palliative treatments in Radiation Oncology				
Q9. Range of delivered doses for treatment of brain metastases:				
2D:	3D:	IMRT:	SRS:	FSRT:
Q10. Number of radiation treatments for cancer emergencies (i.e. mediastinal syndrome and metastatic spinal cord compression) performed in Your Centre between January and December 2014:				
Q11. Percentage of utilization of the following techniques:				
2D:	3D:	IMRT:	SBRT:	
Q12. Range of delivered doses for treatment of cancer emergencies:				
2D:	3D:	IMRT:	SBRT:	
Q13. Number of radiation treatments for lung metastases performed in Your Centre between January and December 2014:				
Q14. Percentage of utilization of the following techniques:				
2D:	3D:	IMRT:	SBRT:	
Q15. Range of delivered doses for treatment lung metastases:				
2D:	3D:	IMRT:	SBRT:	
Q16. Number of radiation treatments for liver metastases performed in Your Centre between January and December 2014:				
Q17. Percentage of utilization of the following techniques:				
2D:	3D:	IMRT:	SBRT:	
Q18. Range of delivered doses for treatment liver metastases:				
2D:	3D:	IMRT:	SBRT:	
Q19. In Your Centre, are palliative radiation treatments performed with concurrent chemo- and/or biological therapy?				
Yes:	No:	Selected cases (specify):		
Q20. Do You use questionnaires for evaluation of quality of life?				
Yes:		No:		
Q21. Do You perform pain evaluation with adequate scales?				
Yes:		No:		
Q22. Do You take active part in the prescription of palliative drugs other than radiation treatment?				
Yes:		No:		
Q23. Do You take active part in a multidisciplinary evaluation for palliative treatments and supportive care?				
Yes:		No:		
Q24. In Your Centre, is there a multidisciplinary group for palliative treatments?				
Yes:		No:		
Q25. Do You use prognostic scores to decide radiation technique and delivered dose?				
Yes:		No:		
Q26. In Your Centre, do You perform re-irradiation?				
Yes:		No:		
Q27. In Your Centre, are patients followed-up?				
Yes:	No:	Selected cases (specify):		

2D — no-conformal radiotherapy; 3D — conformal radiotherapy; IMRT — intensity modulated radiotherapy; SBRT — stereotactic body radiotherapy; SRS — brain radiosurgery; FSRT — brain fractionated stereotactic radiotherapy

RT performed. Subsequent questions were related to RT technique and dose delivered to metastases of bone, brain, lung, and liver in addition to cancer emergencies. Other questions investigated a possible association of chemotherapy and/or biological therapy, pain and quality of life (QoL) evaluation, drugs prescription, prognostic scores adopted and re-irradiation utilization.

Results

Questions ≠ 1–2: General data

Overall, 209 medical doctors filled in the questionnaire. Excluding four who did not communicate their working geographic area, 91(44.4%) were engaged in Northern, 52 (25.4%) in Central

and the remaining 62 (30.2%) in Southern Italy. The median age of participants was 44.4 years.

All 209 participants communicated their length of service, 190 were specialists in Radiotherapy (among these, 53 were heads of Centers) and 19 trainees in Radiotherapy. Although the majority (185/209, 88.5%) of participants responded that the main common symptom requiring palliative RT is pain, palliative RT prescription varied largely between centres ranging from 0 to 70% of all treatments.

Questions ≠ 3–6: Bone metastases

To the questions regarding bone metastases, among 209 participants, 170 (81.3%) colleagues answered and only 2/170 reported they did not perform RT on bone metastases.

As regards the question asking about the type of RT technique adopted, 164 answered to the question and 45 skipped it. Two-dimensional (2D) RT, three-dimensional (3D) RT, intensity modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) average utilization in this setting was 13%, 79%, 12.4% and 6.9%, respectively

(Fig. 1). Total delivered doses for bone metastases ranged from 8 to 45 Gy in 2D-RT, from 8 to 45 Gy in 3D-RT, from 8 to 60 Gy in IMRT and from 8 to 40 Gy in SBRT.

Among 167 participants who responded to the question on the use of Rapid Response Radiotherapy Program in patients with bone metastases, 105/167 (62.9%) adopted this programme in clinical practice and 62/167 (37.1%) did not. The difference between the three Italian areas did not reach statistical significance.

Questions ≠ 7–9: Brain metastases

About the treatment of brain metastases, 155/209 (74.1%) answered the questions: 149/155 (96.1%) treated brain metastases in their clinical practice and the remaining 6/155 (3.9%; 5 from Northern and 1 from Southern Italy) did not. The percentages of techniques adopted were as follows: 2D-RT, 3D-RT, IMRT, brain radiosurgery (SRS) and brain fractionated stereotactic radiotherapy (FSRT) in 21.8%, 70.9%, 11.4%, 18.8% and 10.5%, respectively (Fig. 1). Delivered doses for brain metastases

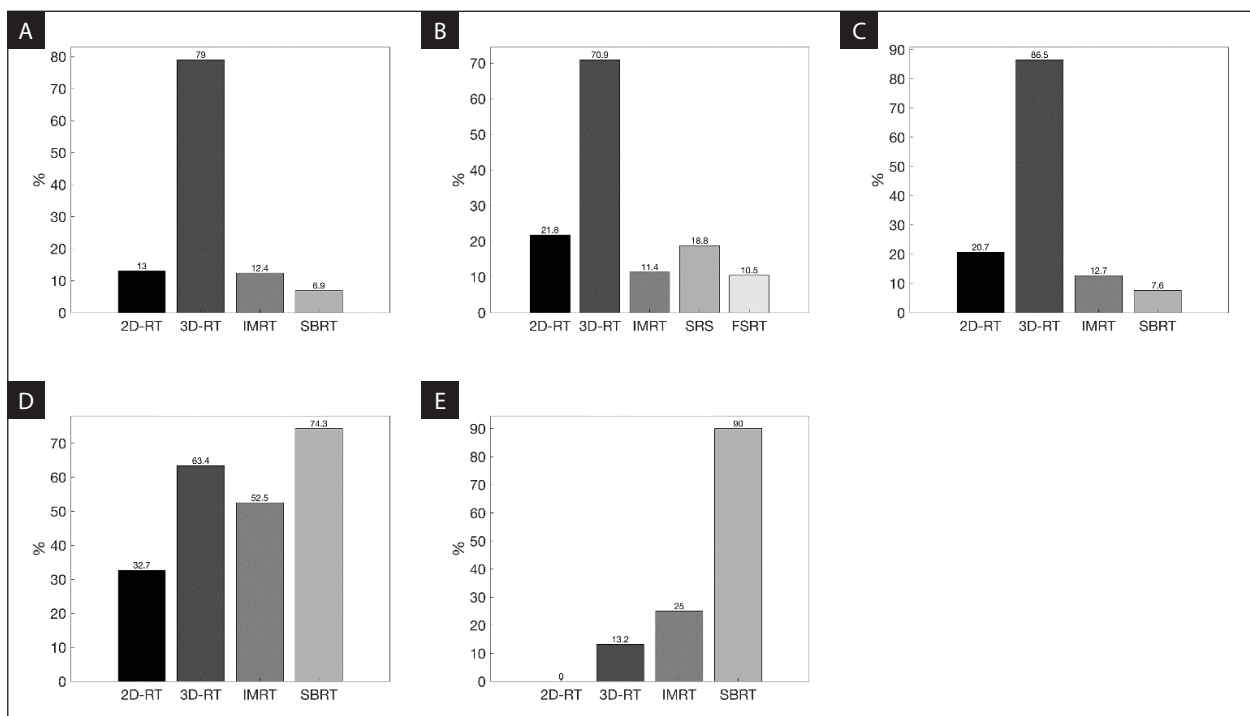


Figure 1. The figure shows the percentage of techniques adopted for bone metastases (A), brain metastases (B), cancer emergencies (C), lung (D) and liver metastases (E). IMRT — intensity modulated radiotherapy; SBRT — stereotactic body radiotherapy; SRS — stereotactic radiosurgery; FSRT — fractionated stereotactic radiotherapy

ranged from 4 to 30 Gy in 2D-RT, from 15 to 45 in 3D-RT, from 4.5 to 50 in IMRT, from 5 to 60 in SRS, and from 10 to 50 in FSRT.

Questions 10–12: Cancer emergencies

150 (71.8%) participants declared to use RT in cancer emergencies, the prescription was generally conditioned by site of tumour, patients' performance status and blood cell count. The main indications for RT in this set of patients were metastatic spinal cord compression and mediastinal syndrome (98% both). Interestingly, 2D-RT technique was adopted only in a minority of cases (20.7%). More complex techniques were generally performed, 3D-RT, IMRT and SBRT in 86.5%, 12.7% and 7.6% of cases, respectively (Fig. 1). The difference between the three Italian areas did not reach statistical significance. The ranges of administered doses for cancer emergencies were 30/36 Gy for 2D-RT techniques, 25/50 Gy for 3D-RT modalities, 25/50 Gy for IMRT, and 30/50 Gy for SBRT. No significant differences emerged between particular geographic Italian areas.

Questions 13–15: Lung metastases

About treatment of lung metastases, there were 147/209 (70.3%) respondents, 103/147 (70.1%) treated lung metastases in their clinical practice and the remaining 44/147 (29.9%) did not. The difference between the three Italian areas did not reach statistical significance. Of 147 respondents, 101 reported the RT technique—with a 2D-RT, 3D-RT, IMRT and SBRT average utilization of 32.7%, 63.4%, 52.5% and 74.3%, respectively (Fig. 1). The ranges of delivered doses were 8/30 Gy for 2D-RT, 8/60 Gy for 3D-RT, 16/70 Gy for IMRT, and 7.5/60 Gy for SBRT.

Questions 16–18: Liver metastases

To the questions on treatment of liver metastases, 146/209 answered, 49/146 (33.6%) treated liver metastases in their clinical practice and the remaining 97/146 (66.4%) did not: the difference between the three Italian areas did not reach statistical significance. Among these 49 who answered the question, 48 communicated the utilized technique: 3D-RT, IMRT and SBRT in 13.2%, 25% and 90%, respectively (Fig. 1). Delivered total doses

for liver metastases ranged from 10 to 100 Gy in 3D-RT modality, from 10 to 75 Gy in IMRT, and from 10 to 75 Gy in SBRT.

Questions 19–22: Multimodality treatments, QoL evaluation, pain assessment & palliative drug prescription

There were 146/209 (69.8%) colleagues who answered these questions. About chemotherapy and/or biological therapy concurrent to RT, 100/146 (68.5%) participants performed these concurrent approaches, 10/146 (6.85%) only in particular cases, whereas the remaining 36 (24.65%) did not. The difference between the three Italian areas reached statistical significance ($\chi^2 = 7.446$; $df = 2$; $p = 0.024$), due to a lower use of multimodality treatments in Central Italy as compared to Northern and Southern Italy.

Quality of life evaluation was done only by 54 of 146 (37%) respondents and the difference between the three Italian areas did not reach statistical significance.

Pain evaluation was performed by 125/146 (85.6%) respondents and the difference between the three Italian areas did not reach statistical significance.

Palliative drugs were administered by 133/146 (91.1%) colleagues and 13/146 (8.9%) did not administer them. No statistically significant difference was registered between the three Italian areas.

Questions 23–25: Multidisciplinary interventions and Prognostic score use

Considering multidisciplinary interventions, 145/209 (69.4%) participants answered the question; 62/145 (42.8%) took part in an oncologic multidisciplinary team for palliative treatments and 83/145 (57.2%) did not. The difference between the three Italian areas did not reach statistical significance. Among them, only 77.3% colleagues answered that they were actively involved in the discussion of the multidisciplinary evaluation, whereas the remaining 22.7% were not.

Prognostic scores were used by 71/145 (48.9%) participants, 5 of these (3.4%) used prognostic scores only in selected cases such as bone and brain metastases. There was no significant difference between Italian geographic areas.

Questions 26–27: Re-irradiation and follow-up

Among 149/209 (71.3%) participants who answered question concerning re-irradiation, 109 (73.2%) performed it, 21 (14%) considered it only in selected cases and 19 (12.8%) did not perform re-irradiation. The difference between the three Italian areas did not reach statistical significance.

To the question on follow-up, 144/209 participants answered, 47/144 (32.6%) followed their patients in all cases, 27/144 (18.8%) only in selected cases (i.e., in accordance with other Specialists or if the patient had no reference) and remaining 70/144 (48.6%) did not follow-up their patients. The difference between the three Italian areas reached statistical significance ($\chi^2 = 19.017$; $df = 2$; $p < 0.001$) because, in clinical practice, in Northern Italy a significantly lower number of Centres follow up patients after palliative RT as compared to Central and Southern Italy.

Discussion

Radiotherapy is generally given with curative or palliative intent. Improvement in RT technology — such as IMRT, SRS and SBRT — together with advances in drug availability (such as biologic therapy and immunotherapy) have blurred the line between palliative and curative intent care for patients with metastatic cancer. Patients who fall into the category of palliative RT have historically been treated with the most convenient and cost-effective RT regimens which were best delivered using minimally complex and hypofractionated courses avoiding iatrogenic toxicity. However, given multiple new reports, palliative RT may now include concurrent goals of symptoms relief, symptom prevention, local tumor control, and possible cure [5, 6]. So, facing the same scenario of a patient with metastatic disease, therapeutic intent and RT prescription can be different depending on the radiation oncologist who takes care of the patient [5]. Prescription of RT doses (single high dose, hypofractionation, long course RT) technique utilized (2D-RT, 3D-RT, IMRT, SRS, SBRT), therapeutic intent (purely palliative intent versus a palliation with the possibility to improve patient survival without pursuing the cure) are variables daily faced by the radiation oncologist in their clinical practice.

To our knowledge, only a few surveys have been published on palliative RT, four were from the United States and only one from Europe [7–11]. Of aforesaid surveys, two were published between 2015 and 2016, while others date back more than 12 years. Recently, Ryu et al. in an international survey of the treatment of metastatic spinal cord compression showed that selection of RT dose and fractionation varied significantly among different continents and countries, while using similar factors to make treatment decision [12].

This article provides data on the utilization of RT among Italian radiation oncologists in the setting of cancer palliation — including bone, brain, lung and liver metastases — in addition to the treatment of emergencies caused by cancer, as well as the attitude of radiation oncologists in evaluating QoL, pain and associated anticancer drugs. Findings resulting in a questionnaire filled by 209 respondents on these topics as well personal characteristics including age, geographic area, length of service and qualification of the participants were analysed.

This survey indicates that modern techniques to deliver irradiation are, indeed, frequently employed in palliative RT. In particular, in the metastatic scenario, SBRT has resulted to be the preferred delivery technique for the treatment of lung and liver metastases, whereas 3D-RT is preferred when treating bone and brain metastases.

Such highly complex RT techniques, while improving local tumour control, demand extra time in planning, simulation, quality assurance and can be a source of higher costs in the health system. In Italy this represents an important issue because our country is based on an “universal” health system which allows free access to all patients. Hence, as the use of technology in the treatment of various palliative scenarios is variable and cost-demanding, further systematic investigation and randomized clinical trials comparing novel highly conformal techniques with conventional ones should be warranted.

While 3D-RT is commonly used for the treatment of bone metastases, our data show significant variability in the dose and fractionation used, ranging from 8 to 45 Gy for 3D-RT, from 8 to 60 Gy for IMRT and from 8 to 40 Gy for SBRT. During the last decades, several studies have shown that a single 8 Gy fraction of RT is equivalent to a multi-fraction course for uncomplicated bone metastases with

regard to pain response. The primary difference between single fraction and multi-fraction RT for uncomplicated bone metastases is double retreatment rate in the single fraction arm compared with the multi-fraction scheme [3]. Recently, the ASTRO guidelines committee has concluded that regimens including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions and 8 Gy in one fraction are equivalent in pain relief for uncomplicated bone metastases and that longer dose-fractionation schemes should not routinely be utilized for the management of uncomplicated bone metastases [4]. Despite these recommendations, our survey highlights that several variations in clinical practice still occurs in this palliative setting.

High heterogeneity has also been found for the treatment of brain metastases. Historically, whole brain RT was the standard of treatment in patients with multiple (i.e., ≥ 3 –4 lesions) brain metastases. However, SRS is emerging as a valuable alternative for patients with multiple lesions encompassing a low tumor volume [13]. In line with these data, our survey shows that 2D-RT and 3D-RT are the most commonly used techniques for the treatment of brain metastases; followed by SRS.

By contrast, the survey highlighted an inverse trend for lung and liver metastases. Previously, the role of RT in this setting of patients had been limited due to the high radiation sensitivity of lung and liver healthy parenchyma and the intrinsic technical limitation in achieving the high radiation doses needed to eradicate metastatic lesions. The SBRT has allowed to deliver a tailored dose to the tumor avoiding irradiation of surrounding healthy tissues, thus playing a major role as a non-invasive but potentially curative treatment option for patients with lung [14] or liver oligometastases [15] who are not eligible for other radical treatments. Indeed, the results of the present survey suggest that SBRT is the most used technique in Italy for the treatment of liver and lung metastases.

The use of SBRT is recently increased also in consideration of the emerging clinical tendency of combining RT with novel systemic agents [16–18]. Indeed, 68.5% of the participants of the survey usually perform this concurrent approach, with a higher prevalence in Central Italy compared with Northern and Southern Italy. Although there is still a lack of high-quality clinical data to guide the care of patients who are treated with novel compounds

in conjunction with RT, combined modality treatment holds potential for enhancing the therapeutic ratio both in curative and palliative settings.

Palliative RT also plays a critical role in the clinical scenario of oncologic emergencies, such as metastatic spinal cord compression and mediastinal syndrome.

For metastatic spinal cord compression, patients with a good performance status, longer life expectancy and lesion that is amenable to surgical intervention, surgery followed by RT should be the standard of care, while for patients who are unfit for surgery, RT alone is the treatment of choice [19]. Maranzano et al. showed that patients with metastatic spinal cord compression and life expectancy < 6 months may benefit from a single fraction of 8 Gy [20]. In discrepancy with these findings, radiation oncologists answering to this survey declare to treat metastatic spinal cord compression mainly by using 3D-RT with doses ranging from 25 to 50 Gy, thus likely suggesting a more common use of long-course regimen over the short-course fractionation.

On the other hand, according to ASTRO practical guidelines for palliation of thoracic symptoms [21], the most commonly used regimen in patients with mediastinal compression is 10×3 Gy.

Regarding re-irradiation, it is possible to affirm that this kind of therapy is delivered by the majority of respondents. This issue has a relatively recent renaissance and could be an important sign of high-quality RT in our country.

Interesting data emerged on follow-up activity where only 51.4% of respondents declare to follow up patients after irradiation, with a significantly lower number of physicians in Northern Italy following up patients after palliative RT as compared to Central and Southern. This could reflect the scarce interest of Italian radiation oncologists in daily clinical practice on follow-up patients with poor prognosis. This attitude can lead to not registering important information on RT efficacy and possible iatrogenic toxicity. As regards geographic differences in follow-up activity, one of the possible explanations as to why a lower percentage of radiation oncologist from Northern Italy do not follow their patients may be that in Northern Italy has the highest number of comprehensive cancer centers where metastatic patients are followed by multidisciplinary teams and the pa-

tient is referred to a radiation oncology unit just for irradiation.

This is the first nationwide study among Italian radiation oncologists evaluating clinical practice related to RT prescribed with palliative intent. An important limitation of this study is the selection bias inherent to the nature of an electronic survey, where the views of those who chose to respond may not be generalizable to all radiation oncologists to whom the questionnaire was submitted. Surely, there are differences among Italian centers regarding the availability of advanced technologies, such as volumetric or serial modulated arc therapy, stereotactic dedicated or not dedicated Linear accelerators, and so on. It is indubitable that every radiation oncologist deliver treatment according to available machine/s and this influence the choice of technique modality to treat different clinical scenarios. For these reasons, some conclusions could be biased. However, all respondents had availability, at least, of the 3D-RT and IMRT technique in their center. In fact, no substantial differences were observed in the three geographical areas (Northern, Central and Southern) regarding the technique used to deliver irradiation.

However, the variety of demographics encompassed by the participants and the variety of professional roles of radiation oncologists, ranging from trainees to head of centres, who answered to the questionnaire of this survey, suggest a relatively representative sample and provide assurance on the validity of our findings.

The obtained data could not be representative of other countries, also considering the national laws that regulate palliative care management. It is worth noting that the data of the present survey were collected in 2016 in order to be presented during a national meeting [22]. We decided to publish these “old” data for two principal reasons. First, despite the fact that most Italian radiotherapy centers had high technology in 2014, in clinical practice, there has not been a “dramatic” change in technology availability. Besides, in 2020, the Italian government issued the so-called Amato decree which allocated one hundred million euro for the modernization of radiotherapy in Southern Italy. This financial program will be completed in August 2022. Hence, we decided to publish data before the completion of this plan of investment.

We planned to repeat this study in 2024 when all Southern centers will have 1-year availability of stereotactic and VMAT techniques. The second reason is that not all Journal readers come from developed countries with a mature economy and technologically advanced infrastructure compared to other nations. In this scenario, every reader may evaluate the results of the present survey according to his/her country economic situation. Finally, we have now decided to publish these relatively recent data due to the lack of studies on this issue in literature.

Conclusions

We believe that the present survey is clinically meaningful in providing a direct and comprehensive overview on the palliative radiotherapy in Italy and highlighting some heterogeneity in radiation oncologists’ practice in metastatic cancer patients’ treatment and follow-up.

Conflicts of interest

All the Authors declare they have no conflict of interest.

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Ethical permission

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