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ORIGINAL ARTICLE

IMproved MAnagement (IM-MA study) in cancer-related pain: the value of a joint approach by an integrated team of radiotherapist and anesthetist

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Abstract

Purpose Purpose of this study was to retrospectively review our experience of multidisciplinary clinic providing a joint approach by radiation oncologist and anesthetist for patients with cancer pain to evaluate the adequacy and the IMprovement in MAnagement (IM-MA study) of this symptom.

Methods A Team for Pain Management (TPM) represented by radiation oncologist and anesthetist weekly provided consultations to patient presenting cancer pain. TPM prospectively reported epidemiologic, symptomatic, and pharmacological data. TPM modified pain therapy and indicated antalgic radiotherapy. Patients were evaluated at baseline and after 4 weeks after intervention.

Results From November 2015 to April 2016, 65 patients were evaluated by TPM. At the baseline, 18 patients (27.7%) were undertreated (i.e., receiving inadequate pain management); furthermore, 27 patients (41.5%) despite receiving strong opioids had uncontrolled pain. After 4 weeks from intervention, undertreated patients were reduced to 1.53%. For those patients undergone to radiotherapy, response at 34 weeks was scored as follows: complete response 28.8%, partial response 46.7%, pain progression 0.95%, indeterminate response 23.8%.

Conclusions A multidisciplinary Team for Pain Management improved the clinical management, optimizing pain control and increasing adequacy of pharmacological management. The TPM intervention seems particularly worth for patients presenting specific features including BTcP, neuropathic pain, severe pain due to bone metastases, and any potential candidate to radiotherapy. Larger series and QoL questionnaires are required to confirm these results.

Keywords Cancer pain · PMI index · Bone metastases · Opioid administration · Palliative radiotherapy · Multidisciplinary pain management

Introduction

Cancer pain is the most recurrent and debilitating symptom and it is often present from the diagnosis [1]. Its prevalence rate is higher than 50% [2]. Although many guidelines have been published since 1986 with the purpose of decreasing the prevalence of inadequately treated pain [3–6], almost half of cancer patients (pts) still receive inappropriate care for pain [7–10], making pain management still a multifactorial challenge for clinicians [11]. A multidisciplinary approach can improve outcomes in terms of symptom control and quality of life and allows the detection of previously unmet needs of both patients and caregivers [12–15]. In our Radiation Oncology Department, a multidisciplinary team for pain management (TPM) represented by radiation oncologists and anesthetists skilled in pain therapy provides a joint approach for cancer-related pain. Purpose of this study is to retrospectively evaluate the efficacy of our TPM by an analysis of changes in pain management index (PMI) to evaluate the IMproved MAnagement (IM-MA study) of the painful condition.

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Materials and methods

Multidisciplinary team and work

We constituted a TPM represented by radiation oncologist and anesthetist belonging to the Hospital Pain Service, to offer a weekly outpatient service to oncological pts presenting cancer-related pain from primitive, secondary lesion, and/or radiotherapy toxicity, or pts without pain but needing to modify antalgic therapy. Patients excluded were those admitted in hospital consultation because they entered a different palliation circuit. The nursing staff automatically entered the visit to patients with cancer pain who required a visit or who were referred to us by other colleagues.

TPM provides indications to treatments, defines timing of interventions, and takes care of outcome's evaluation. Specific activities of the anesthetist-pain therapist include to identify and describe pain syndromes and their characteristics; to detect pain scores; to prescribe or modify analgesic therapy; to prescribe adjuvant drugs for neuropathic pain; to identify opioid toxicity; to prescribe adjuvant and supportive medications (e.g., for constipation and nausea); and to prescribe rescue therapy for breakthrough cancer pain (BTcP). Specific activities of radiation oncologist include to correlate pain with radiological signs of local disease, to provide indication to radiotherapy, to prescribe target volume and fractionation, and to evaluate the response to radiotherapy. TPM provided a written personalized medication schedule to both patient and attending family's members at the end of each clinic consultation.

After 4 weeks from any therapeutic event (both including pharmacological medication, and/or radiotherapy administration), pts were evaluated through a new visit. If necessary due to patient's compliance or logistic, TPM addressed the 4-week evaluation by phone.

Data collection

Data by TPM were prospectively collected at baseline and after a month of therapy (e.g., drugs modification, radiotherapy indication and response).

For all the patients, we collect general epidemiological characteristics: age, Karnofsky Performance Status (KPS), characteristics of disease (primary tumor site, stage of disease, and presence of bone and/or visceral metastases). Specific data regarding cancer pain were also recorded, including topography, type (neuropathic, nociceptive, mixed) and intensity of pain, presence of BTcP, and type of bone lesion (complicated or not) [16]. Non-complicated bone metastases were defined as for absence of complication as fracture, epidural spinal cord compression, and hypercalcemia.

Pain intensity and management evaluation

Pain was measured by an 11-point Numeric Rating Scale for Pain (NRS) assessing the intensity of pain, with "0/10" equivalent to "no pain" and "10/10" equivalent to "worst imaginable pain." [17] Pain intensity was stratified as none (rating = 0), mild (rating 1–4), moderate (rating 5–6), or severe (rating 7–10) [18, 19]. Analgesic consumption was described according WHO scale as "none," "non-opioids," "weak opioids" (e.g., codeine-containing analgesics), and "strong opioids" (e.g., morphine and hydromorphone). Analgesic opioid assumption was recorded and converted through daily oral morphine equivalent [OMED] correlation.

Adequacy of pharmacological pain management was assessed by the Pain Management Index (PMI). Cleeland's PMI is categorized by correlating pain intensity to analgesic consumption [20].

Practically, the patient's level of worst pain is given of a value as follows: "0" (no pain), "1" (mild pain; NRS 1–4,), "2" (moderate pain; NRS 5–6), or 3 (severe pain; NRS 7–10). Then, the pain level is subtracted from the most potent level of analgesic drug therapies as prescribed by the physician, scored as "0" (no analgesic drug), "1" (non-opioid), "2" (weak opioid), or "3" (strong opioid). PMI can range from "− 3" (a patient with severe pain receiving no analgesic drugs) to "+ 3" (a patient receiving morphine or an equivalent and reporting no pain). Negative scores indicate pharmacological undertreatment of pain; scores ≥ 0 indicate acceptable treatment [20].

Endpoints

Primary objective of this study was to evaluate the efficacy of an integrated approach to symptomatic patients in terms of improvement of pain control. Primary endpoint for pain control was NRS reduction at 4 weeks, measured as a change in NRS level (e.g., from "severe" to "moderate" pain). Besides, our study wants to observe the rate of increase of PMI from scores indicating undertreatment (i.e., negative values) to scores indicating acceptable treatment (i.e., non-negative values) after joint approach at 4 weeks. For irradiated symptomatic bone metastases, the evaluated endpoint was the response at 4 weeks according to the International Bone Metastases Consensus Working party Guideline [21, 22].

Results

From November 2015 to April 2016, we evaluated 65 pts for a total of 122 sites of cancer pain referred. Of these pts, global clinical oncological management was referred to our palliative management group for 28 pts (43%), other colleagues of our department for 26 pts (40%), and oncological specialists

present in the hospital (e.g., medical oncologist, gynecologic oncologist) 11 pts (17%). Pts' characteristics and pain features are reported in Tables 1 and 2, respectively. Twenty-one pts (32.3%) presented a de novo metastatic cancer; 28 pts (43.1%) presented an already known metastatic disease; 10 pts (15.4%) presented pain by the primitive tumor during or after neoadjuvant therapies; 6 pts (9.2%) presented local relapse. Among pts affected by bone metastases, 75.2% of analyzed sites were uncomplicated.

After 4 weeks from intervention (i.e., drugs modification and/or end of radiotherapy), all the 65 pts were visited or contacted. Median KPS at baseline and after 4 weeks from intervention was 60% (30–80%) and 70% (40–90), respectively.

Pain prevalence and analgesic prescription

Median NRS at baseline and after 4 weeks from intervention was 7 (0–10) and 3 (0–9), respectively. Moderate to severe pain (i.e., NRS 5–10) was reported by 56 pts (86%) at baseline and 16 pts (25%) after 4 weeks. A comparison of the reported NRS score categories at baseline and follow-up is depicted in Fig. 1. A total of 57 pts (87.69%) at baseline and 60 pts (92.3%) at follow-up had a prescription for analgesics prescribed, with 39 pts (60%) at baseline and 55 pts (84.6%) at follow-up receiving weak or strong opioids.

After 4 weeks from intervention: median OMED was 150.5 mg (1–300 mg), without variation from baseline. Eighteen pts (27%) had a specific prescription for drug targeted to neuropathic pain component at follow-up, including pregabalin or gabapentin (versus 11 pts, 17% at baseline).

After 4 weeks from intervention, 13 pts (15.3%) had a specific prescription for drug targeted for BTcP (versus 6 pts, 9.2% at baseline).

Table 1 Patient's characteristics at baseline (65 pts)

Age	Median 67 (range 31–86)
Gender	Male 38 (58.5%)
	Female 27 (41.5%)
kps	Median kps 60% (range 30–80%)
Primary cancer sites	
GI	19 pts (29.2%)
Lung	16 pts (24.6%)
Breast	10 pts (15.4%)
Genitourinary	10 pts (15.4%)
ORL	6 pts (9.2%)
Other	4 pts (6.2%)
Cancer presentation	
Primitive tumor	16 pts (24.6%)
Metastatic tumor (bone + visceral metastases)	49 pts (75.4%)

After 4 weeks from intervention, opioid therapy side effects were reduced to 4.9% of pts with constipation (versus 11.5% at baseline) and 8.2% of pts with drowsiness (versus 6.5% at baseline). No nausea was reported (versus 1.6% at baseline), neither psychomotor agitation (versus 3.3% at baseline).

Adequacy of pain management

Distribution of PMI at baseline and after 4 weeks is depicted in Fig. 2.

At baseline, median PMI was 0 (range 3/− 3); 18 pts (27.7%) presented a negative PMI (values between − 1 and − 3), receiving undertreated pain management (i.e., presence of pain although no antalgic therapy with opioids); 27 pts (41.5%) presented uncontrolled pain (i.e., presence of pain although antalgic therapy ongoing with opioids). PMI ≥ 0 was reported for 47 pts (72.3%).

At 4 weeks after TPM therapeutically intervention, median PMI was 1 (range − 2/3); 1 pts (1.5%) presented a negative PMI (value − 2) due to persistent pain on 3 different pain cancer sites; this pts was not able to assume strong opioids for clinical conditions. Sixteen pts (24.6%) still presented uncontrolled pain, but of them, 9 pts irradiated on bone metastases presented indication to further radiotherapy on other bone lesions; the other 7 pts were not compliant to other RT or pharmacological implementation. PMI ≥ 0 was reported for 64 pts (98.5%).

At the univariate analysis, PMI was weakly correlated to the Pearson analysis, directly with age ($\rho = 0.0297$) and KPS ($\rho = 0.0137$), while inversely with the RT fractionation used ($\rho = -0.0296$), but multivariate linear regression did not show a significant correlation.

Irradiated bone metastases

All pts with symptomatic bone metastases (46/65) underwent palliative radiotherapy for a total of 101 irradiated clinical target volumes (CTV), as follows: 35/101 (34.65%): 8 Gy/1 fx; 1/101 (%) 15Gy/3Ff (0.99%), 59/101 20 Gy/5 fr, 6/101 CTV (5.94%) with 30Gy/10fr. Prescribed treatment schedules are summarized in Fig. 3. Twelve pts underwent RT on 1 site; 19 pts underwent RT on 2 sites; 11 pts underwent RT on 3 sites; 3 pts underwent RT on 4 sites; only 1 pts underwent RT on 6 sites.

Pain response for irradiated bone metastases varied as follows: a clinical response was reported for 75% of patients. In particular, 13 pts (28%) and 22 pts (47%) reported a complete and partial response, respectively. Conversely, 1 pts (1%) presented pain progression and 10 pts (24%) were indeterminate responders.

Responses are summarized in Table 3.

Table 2 Pain evaluation

Cause of cancer pain	Primitive tumor	7 pts (10.7%)	
	Local relapse	8 pts (12.5%)	
	Metastases	46 pts (70.7%)	
	Radiotherapy toxicity	4 pts (6.1%)	
Global oncological management	Best supportive care	26 pts (40%)	
	Sistemic therapy	39 pts (60%)	
	Bisphosphonates*	17 pts (26.2%)*	
	Chemotherapy*	31 pts (47.7%)*	
	Endocrinetherapy*	9 pts (13.8%)*	
		*Some pts underwent more than one systemic	
		Treatment simultaneously; thus global rate apparently exceeds 100%	
Pain evaluation and management		At baseline	At 4 weeks
Nrs (65 pts)	Mean pain	7.13	2.9
	Median pain	7 range (1–10)	3 range (0–9)
Pharmacological management	Opioid therapy ongoing at first contact	39 pts (60%)	55 pts (84.6%)
	Oral morphine equivalent dose (OMED)	150.5 mg (range 1–300 mg)	150.5 mg (range 1–300 mg)
	BTCP drugs	6 pts (9.23%)	13 pts (15.3%)
	Neuropathic pain drugs	11 pts (17%)	18 pts (27%)
	FANS	13 pts (20%)	11 pts (16.9%)
	Corticosteroids	5 pts (7.7%)	8 pts (12.3%)
Pmi indexstratification	Undertreated pain (pmi < 0)	18 pts (27.7%)	1 pt (1.5%)
	Uncontrolled pain (pmi = 0 with severe pain treated with strong opioids)	27 pts (41.5%)	16 pts (24.6%)
	Treated pain (pmi = 0 with mild/ moderate pain treated with weak opioids or fans or pmi > 0)	20 pts (30.8%)	48 pts (73.8%)

Long-term outcome analysis of pts

Three months NRS data showed 27 pts (64.3%) presented a persistent complete response to previous intervention, without pain symptoms and were addressed to a longer follow-up; 12 pts (28.6%) presented a persistent partial response to intervention with a necessity to modulate the pain therapy; 3 pts (7.1%) showed a progression of pain symptoms (2 pts had primary tumor in site, but they were out of therapies, 1 pts presented a pathological fracture already irradiated); 23 pts (35.3%) were lost at follow-up.

Discussion

Data on pain medications, emerging from the first admission to our TPM (baseline evaluation), confirm data from literature that cancer pain is still an uncontrolled symptom [8] with a high proportion of patients (45 patients, 69%) with severe pain (NRS ≥ 7) requiring an adjustment of medication regimen with an increment in opioid dose from the baseline evaluation.

Many studies have applied the PMI to determine the adequacy of analgesic pain management in cancer patients and to explore various predictors of inadequate pain management [23–25].

The main utility of PMI is to identify patients with negative index, who although are in moderate or even severe pain but are not receiving appropriate analgesic medications [9].

A meta-analysis of 20 studies published between 2007 and 2013 found that the prevalence of inadequate pain management as determined by the PMI ranged from 4 to 68%, with a mean value of 31.8% [25]. This data was recently confirmed in a single series reported by Vuong et al. [24] describing inadequate PMI in 33.3% of observed pts. In our series, 28% of pts at first contact with the TPM were found to be undertreated for pain (being classified at baseline evaluation as negative PMI), confirming data from literature.

The undertreatment of pain-related cancer is worldwide depending on many clinical, logistic, and socioeconomic reasons. Factors determining such inadequacy include a suboptimal assessment of pain and its characteristics, reluctance for physicians to prescribe and pts to use opioids because of their known side effects, awareness of the issue by pts and

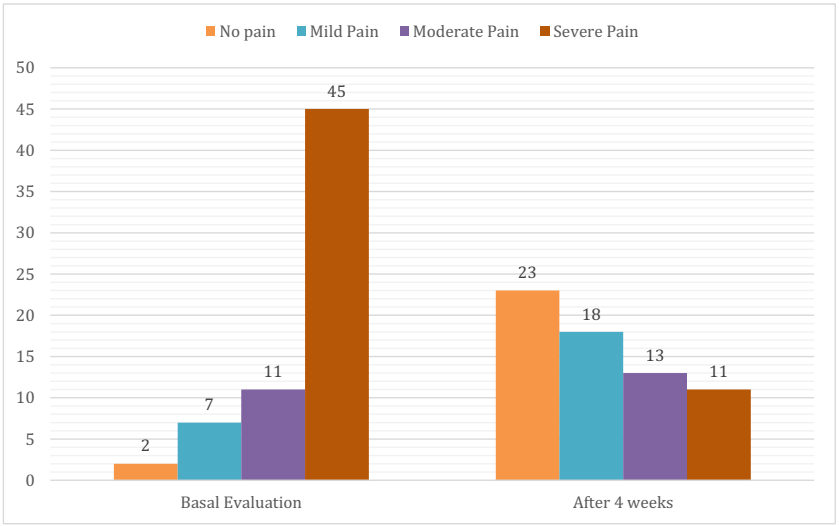


Fig. 1 NRS score category reported at basal line and after 4 weeks for pts evaluated (no pain, NRS 0; mild pain, NRS 1–3; moderate pain, NRS 5–6; severe pain, NRS 7–10)

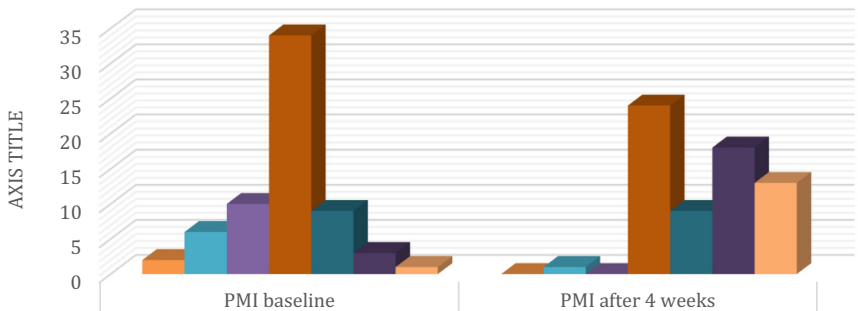
clinicians, and sociocultural factors [8, 26]. In addition, the management of outpatients with cancer pain is influenced by difficulty to get access to specialist consultation, organizational fragmentation of care stream among different specialties, and not at least, logistics of palliative interventions like radiotherapy.

The high prevalence of uncontrolled pain in bone metastases prior to palliative radiotherapy highlights the importance of an interdisciplinary systematic approach to symptomatic patients.

Implementation of integrated clinical pathways for cancer pain management in the oncological practice could improve compliance, providing several benefits: improvement of the quality of pain management, higher adherence to the available guidelines for pain management, promotion of early management of severe pain, and personalization of intervention, including additional supportive care focusing on specific needs of patient and caregiver [8, 12, 13, 15].

The present study shows that an integrated approach to symptomatic patients by TPM has a clear impact on their clinical outcome. TPM intervention reduced pain intensity, decreasing NRS scores corresponding to severe pain and increasing the rates of absent or mild pain (Fig. 1) and improved adequacy of pain management, reducing the rates of negative PMI that reflects a pain management characterized by "undertreatment" (Fig. 2).

In fact, we evaluated at 4 weeks the PMI status with a specific focus on the population initially presenting a negative value, and the proportion of undertreatment was sensibly reduced, approaching 1.5%. The reduction of negative PMI values is understandably very sensitive to the administration of opioids, thus easily obtainable by simple introduction of



	PMI baseline	PMI after 4 weeks
PMI -3	2	0
PMI -2	6	1
PMI -1	10	0
PMI 0	34	24
PMI 1	9	9
PMI 2	3	18
PMI 3	1	13

Fig. 2 PMI at basal line and after 4 weeks on the evaluated pts

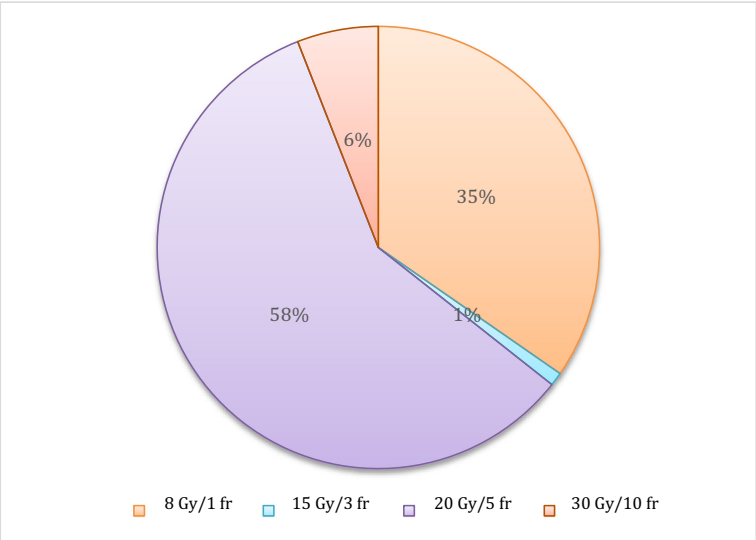


Fig. 3 RT dose distribution for treatment of bone metastases

such drugs into the medical prescription. After intervention, the improvement of the rate of undertreated pts in our series after joint approach (1.35%) is even better than the value reported in literature by some Authors (5%) [27]; although it should be noticed that the study of Apolone et al. only applied pharmacologic approach. PMI score has some well-known drawbacks [23, 24]: it only provides a rough estimate of how pain is treated, taking into account the intensity of pain and the most potent prescribed opioid. The congruence between pain intensity and analgesic therapy described by PMI is a necessary but not sufficient condition to guarantee good pain control.

In fact, despite receiving strong opioids (indicating good pain control according to PMI), a substantial proportion of pts (30.7–85%) still suffer from uncontrolled pain [9, 28] depending on variables related to individual pts and pain characteristics. Also, in our series, despite already having been prescribed and assuming strong opioids for severe pain (thus scored as PMI 0, indicating adequately managed pain), 41.5% of pts still presented severe pain (defined as "uncontrolled" at baseline evaluation). Refractory pain is still an open issue in cancer pain therapy, and a possible development of TPM should be the option for invasive approaches.

These data emphasize that some clinical situations with uncontrolled pain should be treated with a personalized approach: rescue drugs for BTcP, specific agents targeted to neuropathic pain, administration of radiotherapy, and bisphosphonates for symptomatic bone metastases with NRS ≥ 7 [26]. Palliative radiotherapy is a well-recognized therapeutic strategy for symptomatic bone metastases, also with short temporal effort by pts and good results [26]. In our series, we obtained about 75% of response on symptoms after 4 weeks from radiotherapy according to the Response categories according to the International Consensus working party Guidelines [22].

Interestingly, 24% of treatments were referable to the subgroups of "indeterminate response" (according to the International Consensus working party Guidelines [22]) indicating pts experiencing pain relief at irradiate site after

Table 3 Distribution according to response categories according to the International Consensus Working Party Guidelines [22]

Complete response (CR) "A pain score of 0 at treated site with no concomitant increase in analgesic intake (stable or reducing analgesics in OMED)"	13 pts (28%)
Partial response (PR) "Pain reduction of 2 or more at the treated site on a scale of 0 to 10 scale without analgesic increase, or analgesic reduction of 25% or more from baseline without an increase in pain"	22 pts (47%)
Pain progression (PP) "Increase in pain score of 2 or more above the baseline at the treated site with stable OMED, or an increase in OMED compared with baseline with the pain score stable or 1 point above baseline"	1 pts (1%)
Indeterminate response "Any response that is not captured by the complete response, partial response or pain progression definition"	10 pts (24%)

radiotherapy, without reduction of analgesic intake. The most reasonable motivation of this finding could be the complexity of clinical scenario for the subgroup of pts presenting cancer pain often associated to with multiple painful sites. In our series, 22 pts (34%) presented more than 1 symptomatic site at the baseline evaluation.

Conclusion

Our experience of routine clinical approach to pts presenting cancer pain by an integrated TPM showed an improved pain control and increased adequacy of pharmacological management. Of note, TPM, by integrating pharmacological and radiotherapy intervention, particularly improved the clinical outcome for the subset of bone metastatic pts presenting uncontrolled pain in spite of previously prescribed proper pharmacological therapy. Finally, the TPM intervention seems particularly worth for pts presenting specific features including BTcP, neuropathic pain, severe pain due to bone metastases, and any potential candidate to radiotherapy.

Keep in contact with the outpatients by a progressive follow-up or telephonic approach could represent an added value to validate results of the clinical approach and allows maintaining the homogeneity of pharmacological therapy. Moreover, it could make easier the early access to TPM new intervention, if needed. The still high percentage of non-responders to pharmacological therapies should be early addressed with invasive techniques. Further development of such model should introduce other specialists (e.g., psychologist, occupational therapist, physiotherapist, complementary therapy, and social workers) to better frame patient's needs; moreover, including self-report on symptoms could allow to easily and faster interact with our pts. Larger series and QoL questionnaires are required to confirm these results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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