From predictions to practice: value of prediction models for personalised sarcoma care

Kruiswijk, A.A.

Chapter 3

Evaluating the effectiveness of a risk prediction model (PERSARC) on the quality of treatment decisions in soft-tissue sarcomas patients: the VALUE-PERSARC study

Anouk A. Kruiswijk[12], Perla J. Marang-van de Mheen[3], Lisa A.E. Vlug[1], Ellen G. Engelhardt[4], Marta Fiocco[56], Rick L. Haas[78], Yvonne M. Schrage[9], Cornelis Verhoef[10], Marc H.A. Bemelmans[11], Robert-Jan van Ginkel[12], Johannes J. Bonenkamp[13], Arjen J. Witkamp[14], Michiel A.J. van de Sande[2], Leti van Bodegom-Vos[1], VALUE-PERSARC research group.

1. Department of Biomedical Data Sciences, Medical Decision Making, Leiden University Medical Center, Leiden, The Netherlands.
2. Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands
3. Safety & Security Science, Faculty of Technology, Policy & Management, Delft University of Technology, Delft, The Netherlands.
4. Division of Psychosocial Research and Epidemiology/Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
5. Mathematical Institute, Leiden University, Leiden, The Netherlands.
6. Department of Biomedical Data Sciences, Section Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands.
7. Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands
8. Department of Radiotherapy, Leiden University Medical Center, Leiden, The Netherlands.
9. Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
10. Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, Erasmus Medical Center, Rotterdam, The Netherlands.
11. Department of Surgical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands.
12. Department of Surgical Oncology, University Medical Center Groningen, Groningen; The Netherlands.
13. Department of Surgery, Radboud University Medical Center, Nijmegen, The Netherlands.
14. Department of Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands.

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Abstract

Introduction

Risk-prediction models (RPM) can potentially improve treatment decisions by providing personalised survival estimates for different treatment options, but their effectiveness is uncertain. The VALUE-PERSARC study evaluated the impact of the PERsonalised SARcoma Care (or PERSARC) RPM on decision-making quality in patients with high-grade extremity soft tissue sarcomas (STS).

Methods

A parallel cluster randomized controlled trial was conducted in seven Dutch hospitals. Hospitals were assigned to usual care (control) or care with PERSARC (intervention), which guided treatment recommendations and informed patients about personalised risks and relevant treatment options. The primary outcome was decision-making quality, measured by patients' knowledge of risks and benefits of treatment options and decisional conflict (Decisional Conflict Scale). Secondary outcomes included the Cancer Worry Scale (CWS), Shared Decision-Making (SDM-Q9), number of treatment options discussed and treatment choice.

Results

This study enrolled 120 patients -53 patients in the control group and 67 patients in the intervention group. No significant differences were found between the control and intervention groups in patients' adequate knowledge (respectively 82% vs 86%) and decisional conflict (respectively 23.1 [15.5] vs 18.9 [12.8]). CWS (11.7 [3.3] vs 11.0 [3.5]), SDM-Q9 (13.3 [4.0] vs 15.6 [3.3]). Treatment choice also showed no significant differences, though clinicians in the control group were significantly less likely to discuss two or more treatment options (35% vs 93%).

Conclusion

The PERSARC RPM had no statistically significant effect on the treatment decision quality in high-grade extremity STS patients.

Introduction

Soft-tissue sarcomas (STS) are a rare and diverse group of tumours accounting for approximately 1% of all adult cancers [1] with an estimated incidence of 4 to 5 cases per 100,000 people annually [2]. STS can develop in any anatomical site but most commonly occur in the extremities (60%) [3]. Over 60% of these cases are high-grade, aggressive subtypes, associated with poor outcomes, including a 10% rate of local recurrence, a 50% rate of distant metastases, and a 45% five-year survival rate [4-6].

The primary treatment for high-grade extremity STS typically involves surgery and/or (neo) adjuvant radiotherapy. Each option comes with distinct benefits and risks, and there is no clear consensus on the optimal approach. For instance, while achieving tumour-free resection margin during surgery may improve survival, it can impair quality of life by affecting limb function [6-8]. Conversely, (neo)adjuvant radiotherapy (RT) may allow for narrower surgical margins, preserving function without compromising survival, but it carries risks of side effects like infections, wound healing problems, and radiation-induced functional deficits [9-11].

Given the lack of conclusive evidence on the optimal treatment approach [12, 13], and the different perceptions of risks and benefits by professionals and patients, decision-making for STS patients should ideally involve an assessment of each option including personalised risks. Currently, treatment decisions are often based on standard information, which limits patients' ability to weigh the benefits and risks tailored to their own circumstances. This can lead to decisions that may not align with patients' preferences, increased uncertainty and decisional conflict about which treatment is best for their personal situation [14].

Decision support tools, such as risk-prediction models (RPMs), can provide personalised prognostic information, potentially improving decision quality by helping patients to understand their individual risks and benefits and facilitating more active participation in treatment decision-making [15-17]. To address the need for personalised information for STS patients, our research group developed and validated an RPM (PERsonalised SARcoma Care (PERSARC))[18-20], which provides individualised risk estimates for each treatment option based on factors such as patient's age, tumour size, depth and histology. Previous studies have shown that PERSARC enables clinicians to more accurately predict local recurrence (LR) and overall survival (OS) for individual STS patients [21], potentially leading to more patients opting for limb-sparing procedures without sacrificing survival outcomes. However, it is unclear whether using PERSARC in patient consultations improves patients' decision quality.

Therefore, the VALUE-PERSARC study aimed to evaluate whether PERSARC enhances decision-making by improving patients' knowledge of personalised risks and reducing decisional conflict. We hypothesized that PERSARC would promote informed discussions between STS patients and clinicians, leading to better knowledge and decisions more aligned with patient's values and goals and reduced decisional conflict.

Methods

This parallel cluster randomized controlled trial (parallel CRT) compared usual care without use of the PERSARC RPM to care where the PERSARC RPM was used during multidisciplinary tumour boards and during clinical consultation to assess the impact of these approaches on patients' decision quality. The Medical Ethical Committee Leiden-Den Haag-Delft (METC-LDD) and six other participating Dutch sarcoma centers approved all study procedures (NL76563.058.21). The VALUE-PERSARC study was initially registered in the Netherlands Trial Register (NL9160) on January 8, 2021, and subsequently updated in ClincicalTrials.gov (NCT05741944) on January 31, 2023. The VALUE-PERSARC study protocol has been described previously [22]. The study followed the Consolidated Standards of Reporting Trials (CONSORT) extension guideline for reporting parallel cluster randomized trials [23].

Design and randomization

In the parallel CRT design, participating hospitals (i.e., clusters) were randomly assigned to the control or intervention group (Table 1). Six of the seven participating hospitals are STS expertise centers that collectively treat approximately 85% of the high-grade extremity STS patients in the Netherlands. Randomization was performed by an independent statistician not involved in the study's operations prior to data collection. Due to the nature of the intervention, blinding of allocation was not feasible.

Table 1. Parallel CRT

Inclusion and follow-up patients (n=120)

Hospital	Time
STS center 1	***control***
STS center 2	
STS center 3	
STS center 4	
STS center 5	***intervention***
STS center 6	
STS center 7	

Control condition; usual care. Intervention condition; usual care + PERSARC. CRT; cluster randomized control trial. STS; soft-tissue sarcoma.

Study population and recruitment

The study included individuals aged 18 years or older who were newly diagnosed (histologically confirmed) with high-grade extremity STS, and had no predetermined treatment plan. High-grade was defined according to the Fédération Nationale des Centres de Lutte Contre le Cancer grade II and III[24]. Eligible sarcoma subtypes were those covered by the PERSARC model, including high- grade angiosarcoma, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell sarcoma, myxofibrosarcoma, (myxoid) liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma, (pleomorphic) STS not otherwise specified, malignant rhabdoid tumour, alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, rhabdomyosarcoma and conventional fibrosarcoma. Patients undergoing treatment with non-curative intent or requiring other treatment modalities than surgery and/or radiotherapy were excluded from the study. To participate, all patients were required to download the VALUE-PERSARC app on their personal mobile devices, available through the App Store and Google Play Store.

The recruitment process of patients was identical for the hospitals in the control and intervention group. Eligible patients received information about the study from their treating physician and/or specialist nurse. After providing signed informed consent, patients were given an activation code by their physician to enable the VALUE-PERSARC app. This code automatically assigned patients to the randomized hospital condition, either control or intervention.

Intervention

The VALUE-PERSARC app was also used for data collection purposes. For patients in the control group, the app did not include the PERSARC RPM (Supplementary file 1); it was only used to collect baseline characteristics, such as patients age and tumour type, and included questionnaires to gather outcome data. In the intervention group, the VALUE-PERSARC app included the PERSARC RPM which was integrated into usual care at two key points in the decision-making process. First, STS clinicians used PERSARC predictions during multidisciplinary tumour board (MTB) meetings to guide treatment recommendations. Second, the oncological or orthopedic surgeon utilized PERSARC prediction during patient consultations to explain the diagnosis and discuss the benefits and risks of all relevant treatment options. The VALUE-PERSARC app was specifically designed to be patient-friendly and provided prognostic estimates for each treatment option based on the characteristics of the individual patient (Supplementary file 1). Once a patient was assigned to control or intervention group and set up their account, they remained in that version of the app for the duration of the study.

Blinding

Patients were given general information about the study's purpose, which was described as comparing different approaches to communicating treatment risks and benefits. Specific details about the study design and intervention were not disclosed to prevent bias in patients' responses based on their group assignment. Due to the nature of the intervention, it was not possible to blind clinicians treating STS patients. Researchers were not blinded for practical reasons, such as when assistance was needed in installing the VALUE-PERSARC app.

Outcome measures

The primary outcome, decision-making quality, was assessed one week after the treatment decision using questionnaires. It included two components: patients' adequate knowledge of risks and benefits of each treatment option and experienced decisional conflict. Patients' knowledge was evaluated with a self-developed, STS-specific, 6-item knowledge questionnaire (Supplementary file 2). Patients' knowledge was dichotomized (i.e., adequate vs. inadequate). In this study, knowledge was considered adequate if at least 50% of the statements were answered correctly, corresponding to a score of ≥3 out of 6 [22]. Decisional conflict was assessed using the Decisional Conflict Scale (scored 0-100), where scores below 25 indicate the ability to implement a decision, while scores above 37.5 suggest decision delay. Higher scores reflect greater conflict [15].

Secondary outcomes included cancer-related worry (measured using the Cancer Worry Scale (scored 0-100, with higher scores indicating greater worry)[25] and patients' perception of their involvement in decision-making, assessed using the Shared Decision Making (SDM-Q-9) (scored 0-100, with higher scores indicating a higher level of experienced SDM)[26]. These outcomes were evaluated one week after the treatment decision. Other secondary outcomes included the anticipated treatment choice (i.e., surgery and/or (neo)adjuvant radiotherapy) and the number of treatment options discussed. The latter was collected through a checklist send to clinicians after each consultation. Clinicians were asked to indicate how many and which treatment options were discussed during the consultation. The number of treatment options was then dichotomized into one or two or more options to allow for multilevel analysis. The checklist was e-mailed immediately after each patient consultation, with reminders sent after one week (Supplementary file 3).

Sample size

The sample size calculation is described in more detail in the study protocol [22]. The sample size calculation was based on the Decisional Conflict Scale, with previous research reporting effect sizes for interventions ranging from 0.4 to 1.2 [15]. Drawing from similar studies involving cancer patients, we assumed a conservative mean difference of 0.30 and a standard deviation of 0.5, resulting in an effect size of 0.6 [27, 28]. To achieve 80% power and taking

into account an intraclass correlation coefficient of 0.1, we estimated that 52 participants per group (104 in total) would be required. Allowing for a 10% loss to follow-up, we aimed to recruit at least 120 patients.

Statistical analysis

An intention-to-treat approach was used for all analyses. Since randomization was conducted at hospital level, baseline patient characteristics (age, gender, ASA physical status classification, educational level) and tumour characteristics (size, depth, grade, location, and histological subtype) were compared between study groups. Differences between groups were assessed using t-tests for continuous variables and $\chi 2$ tests for categorical variables. If the assumption of normality was violated, a non-parametric test was applied.

Sum scores for the DCS, CWS, and SDM-Q-9 questionnaires were calculated according to their respective manuals [15, 25, 26]. Primary and secondary outcomes were analysed using multilevel regression models, incorporating hospital as a random effect. For the knowledge outcome and the number of treatment options discussed, a generalized linear mixed model with a logit link function was used to account for the binary nature of these outcomes. Mean differences were reported for continuous outcomes, while odds ratios and standard errors were provided for dichotomous outcomes. All analyses were performed using the R software environment [29], and a two-sided p-value ≤ 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled between August 2021 and August 2024 across seven centers in the Netherlands. In the control group, 53 patients were included (28 [53%] men; mean [SD] age, 62 [13] years). In the intervention group, 67 patients were included (38 [57%] men; mean [SD] age, 58 [15] years). In the control group, 6% of the patients had a lower level of education, 48% had a middle level, and 25% had a high level. In the intervention group, these percentages were 7%, 37%, and 31%, respectively. Patient and tumour characteristics were similar between the two groups, except for tumour grade ($p < 0.01$) (Table 2). In the control group, 7% of the patients had a lower level of education, 60% had a middle level, and 33% had a high level. In the intervention group, these percentages were 10%, 49%, and 41%, respectively. Patient and tumour characteristics were similar between the two groups, except for tumour grade ($p < 0.01$) (Table 2).

Both the control and intervention groups reported low levels of decisional conflict. The unadjusted mean total score in the Decisional Conflict Scale was 23.1 [SD 15.5] in the control group and 18.9 [SD 12.8] in the intervention group, with no significant difference between the two groups (mean difference: -4.2; 95% CI :-9.3, 0.9) (Table 3). Additionally, no significant differences were observed on any DCS subscale. Most patients in both the control and intervention groups demonstrated adequate decision adequate knowledge (82% in the control group vs. 86% in the intervention group), with no significant difference between the groups (OR 1.4; 95%CI: 0.5, 3.7).

Similarly, there were no statistically significant differences between the control and the intervention groups in terms of cancer worry (mean score: 11.7 [SD 3.3] vs 11.0 [SD 3.5]) or patients' perceived of involvement in shared decision-making (mean score 13.3 [SD 4.0] vs 15.6 [SD 3.3]). However, clinicians reported significantly more often discussing two or more treatment options with patients in the intervention group compared with the control group (93% vs 35%, OR 63.9; 95%CI: 1.2, 3507.5). Despite this, nearly all patients received surgery with pre-operative radiotherapy (89% vs 88%), with no differences observed between the study groups.

Table 2. Patient and tumour characteristics

Characteristics	Control (n=53)	Intervention (n=67)	P value
Age, mean (SD)	62±13	58±15	0.1
Sex			
Male (%)	28 (53%)	38 (57%)	0.8
Educational level			
Low	3 (7%)	5 (10%)	0.7*
Middle	25 (60%)	25 (49%)	
High	14 (33%)	21 (41%)	
Missing	11	16	
Histological subtype			
Myxofibrosarcoma	18 (34%)	15 (22%)	0.1*
MFH/UPS and NOS	9 (17%)	17 (25%)	
Myxoid liposarcoma	6 (11%)	16 (24%)	
Dedifferentiated / Pleomorphic liposarcoma	7 (13%)	3 (4%)	
Leiomyosarcoma	4 (8%)	3 (4%)	
MPNST	1 (2%)	5 (8%)	
Spindle cell sarcoma	3 (6%)	-	
Synovia sarcoma	-	2 (3%)	
Others	5 (9%)	6 (9%)	
Tumour size, mean (SD)	9±5	9±5	0.1
Tumour depth			
Superficial	15 (28%)	27 (40%)	0.2
Deep	38 (72%)	40 (60%)	
Tumour grade			
2	17 (32%)	46 (69%)	< 0.01
3	36 (68%)	21 (31%)	
Location			
Upper extremity	8 (15%)	15 (22%)	0.4
Lower extremity	45 (85%)	52 (78%)	
ASA score			
0	41 (77%)	59 (88%)	0.4
1	9 (17%)	7 (10%)	
≥2	3 (6%)	1 (2%)	

**Fisher's exact test.*

Table 3. Results of primary and secondary outcome measures.

Outcome measure	Control Mean [SD] N = 53	Intervention Mean [SD] N = 67	Model based difference between intervention and control (95%CI)
Decisional Conflict Scale (DCS)	23.1+15.5	18.9+12.8	-4.2 (-9.3, 0.9)
Subscales			
Informed	23.2+16.0	19.4+14.4	-3.8 (-9.3, 1.7)
Value clarity	26.9+16.6	22.2+15.9	-4.7 (-10.5, 1.1)
Support	19.4+15.9	16.3+14.3	-3.1 (-8.5, 2.3)
Uncertainty	24.4+18.3	19.0+14.2	-3.9 (-11.6, 3.7)
Effective decision	22.0+17.7	18.0+14.0	-4.0 (-9.7, 1.6)
missing	2	-	
Cancer Worry Scale (CWS)	11.7 +3.3	11.0 +3.5	-0.6 (-1.9, 0.6)
missing	2	-	
Shared Decision-Making (SDM-Q-9)	13.3+4.0	15.6+3.3	1.8 (-0.8, 4.4)
missing	3	2	
	Control (n(%))	Intervention (n(%))	OR (95% CI)
Adequate knowledge			1.4 (0.5, 3.7)
No	9 (18%)	9 (14%)	
Yes	42 (82%)	56 (86%)	
missing	2	2	
Treatment options discussed			63.9 (1.2, 3507.5)
One	26 (65%)	3 (7%)	
Two or more	14 (35%)	42 (93%)	
missing*	13	22	
*Options***			
R0	9 (22%)	40 (93%)	
R0+pre-op RT	37 (90%)	44 (100%)	
R0+post-op RT	6 (15%)	17 (40%)	
R1-2	1 (2%)	5 (12%)	
R1-2+pre-op RT	6 (15%)	10 (23%)	
R1-2+post-op RT	3 (7%)	3 (7%)	
missing	13	22	
Treatment choice			
R0	5 (9%)	6 (9%)	
R0+pre-op RT	47 (89%)	59 (88%)	
R0+post-op RT	-	1 (2%)	
R1-2	-	-	
R1-2+pre-op RT	1 (2%)	1 (2%)	
R1-2+post-op RT	-	-	
missing	-	-	

**Completed checklists in control group: center 1 (19/19), center 2 (12/18), center 3 (8/13), center 4 (1/3). Completed checklists in intervention group: center 4 (24/37), center 5 (18/24), center 7 (1/3). **these percentages do not add up to 100% as multiple options were possible.*

Discussion

The VALUE-PERSARC study found that integrating the PERSARC RPM into the decision-making process of patients with soft-tissue sarcoma did not enhance the decision quality. Specifically, it did not improve patients' knowledge of treatment risks and benefits or reduce decisional conflict. Additionally, there was no statistically significant difference in cancer worry, patients' perceived level of shared decision-making or treatment choice. However, clinicians in the intervention group reported discussing more treatment options compared with the control group.

Over the past few decades, numerous risk prediction models (RPMs), such as PERSARC, have been developed, updated and validated to support medical decision-making [30-33]. These models are often evaluated solely on their statistical performance, while their integration into clinical practice involves more complex decision-making processes, such as determining the added value of (neo)adjuvant therapies in collaboration with patients but also incorporation in the workflow of clinicians. Therefore, using an RPM in clinical consultations should be viewed as an intervention in itself, and its impact on clinical decisions and, ultimately, on patient outcomes should be assessed [34]. Although the importance of such evaluations is increasingly recognized, studies examining the impact of RPMs on (shared) decision-making and patient outcomes are still rare and often considered difficult to implement [30, 34-36]. To the best of our knowledge, this is the first clinical validation study that evaluated the effect of an RPM in terms of decision quality from patients' perspective in the context of sarcoma care.

The PERSARC RPM, integrated into the VALUE-PERSARC app, was designed to foster deliberation between STS patients and clinicians, with the aim of improving patients' understanding of the treatment risks and benefits. This approach intended to facilitate treatment decisions that align more closely with patients' values and goals, thereby reducing decisional conflict. However, while clinicians in the intervention group discussed significantly more treatment options, this did not translate into improved patient outcomes. The lack of effect observed may be attributed to the improper use of PERSARC in the clinical consultation in the intervention group, as demonstrated in a convergent mixed-methods study conducted alongside the trial [37]. This study revealed that PERSARC was primarily used to support and confirm clinicians' preferred treatment plans rather than promote (shared) decision-making. So, while PERSARC was intended to encourage patient deliberation and help weigh treatment risks and benefits, it often resulted in implicit steering by clinicians towards a specific treatment option, leaving patients feeling they had no genuine choice. Moreover, if patients were not made aware of or not encouraged to consider alternative treatment options, they were less likely to improve their knowledge of risks and benefits of treatment options or to experience any decisional conflict.

These results align with broader literature on decision supporting interventions, such as decision aids, where clinicians frequently fail to properly elicit patients' values and preferences to guide treatment decisions, even when using such tools [37-40]. They also highlight that simply introducing a tool like PERSARC is insufficient. Clinicians need additional guidance on how to effectively use these tools, including strategies for communicating risk estimates and conducting well-structured consultations (i.e., making more effective and efficient use of consultation time), to truly facilitate informed/shared decision-making.

Implications

The success of using RPMs to support personalised decision-making in clinical encounters relies on recognizing patients' values, opinions, and treatment preferences which may differ from those of clinicians [41]. Therefore, it is essential to discuss viable treatment options in a neutral manner, adhering to the principles of shared decision-making. This allows patients to adequately weigh treatment risks and benefits and make informed choices that align with their personal circumstances. So, when using RPMs to personalize decision-making, it is essential to combine this use with proper application of SDM, only then will the use of RPMs truly impact treatment decisions.

Strength and limitations

To our knowledge, this is the first clinical validation study evaluating the impact of RPMs on patients' decision quality during clinical consultation. However, several limitations should be noted. First, a key limitation of our study was the high number of missing values in the clinician checklist, as many did not report which or how many treatment options were discussed. Nevertheless, these missing data were evenly distributed across hospitals and conditions, making it unlikely that they had a substantial impact on our results. Second, there is potential selection bias, as clinicians may have enrolled a selective group of patients into the clinical trial, rather than including all patients they encounter in daily practice. For example, older patients may have been underrepresented, particularly if clinicians were uncertain about the added value of radiotherapy, even when PERSARC indicated that it could be helpful for them. Third, while evidence is growing regarding the effectiveness of decision support tools, including RPMs, in improving quality of care and decision-making processes, there is currently no consensus or standardization in measuring either the decision-making process or decision quality [42]. For instance, the use of decisional conflict as an endpoint is debated - careful deliberation on treatment options and personal values may increase conflict rather than reduce it, even though it reflect a more informed decision-making process [43]. This lack of standardization of outcomes measures complicates the interpretation of our results and makes comparison with other studies challenging.

Conclusion

In conclusion, while RPMs like PERSARC hold promise for improving decision-making, their implementation in clinical consultation appears to be challenging, which limits the ability to fully assess their impact on patient outcomes. In this study, the PERSARC RPM did not demonstrate a statistically significant effect on the quality of treatment decisions for patients with high-grade STS in the extremities. This is likely due to the improper use of PERSARC during the consultations. Simply introducing RPMs in clinical practice is not enough; clinicians need additional guidance on effective use, including strategies for communicating risk estimates to better support decision-making.

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Supplementary files

Supplementary file 1

Figure 1. Screenshot app control condition. Without tab 'behandelopties' (without prediction model)

Figure 2. Survival probabilities and risk of LR as displayed within the app in intervention condition

Supplementary file 2

STS specific knowledge questionnaire

General items:

1. According to the medical specialist, it is completely clear what the best treatment is for malignant soft tissue tumours (sarcomas) (incorrect)
2. There are different treatment options possible for my tumour (correct)

Specific items:

3. The more healthy tissue that is excised when my tumour is removed, the better my chance of surviving my disease (correct)
4. The more healthy tissue that is excised when my tumour is removed, the better the function of my arm or leg (incorrect)
5. Radiation therapy before or after surgery can cause wound healing problems (correct)
6. Radiation therapy before or after surgery may affect the function of my arm or leg (correct)

Supplementary file 3

Checklist orthopaedic/oncological surgeon

To be filled in by orthopaedic/oncological surgeon:

1. In which hospital is the patient being treated? …..

2. What was the date of the consultation: …

3. Did you use the PERSARC RPM during the multidisciplinary tumour board meeting?

❑ No ❑ Yes, specifically for:

❑ 1 treatment option ❑ 2 or more treatment options

4. Did you discuss the outcomes of the PERSARC RPM with the patient during consultation?

❑ No ❑ Yes, specifically for:

❑ 1 treatment option ❑ 2 or more treatment options

5. To what extent do you feel the patient understood the risk information?

Did not understand Completely understood

1 2 3 4 5 6 7 8 9 1 0