



Sparano, F., Aaronson, N. K., Sprangers, M., Fayers, P., Pusic, A., Kieffer, J. M., ... Efficace, F. (2019). Inclusion of Older Patients with Cancer in Randomized Controlled Trials with Patient-Reported Outcomes: a Systematic Review. *BMJ Supportive and Palliative Care*, 9, 451 - 463.
<https://doi.org/10.1136/bmjspcare-2019-001902>

Peer reviewed version

License (if available):
CC BY-NC

Link to published version (if available):
[10.1136/bmjspcare-2019-001902](https://doi.org/10.1136/bmjspcare-2019-001902)

[Link to publication record in Explore Bristol Research](#)
PDF-document

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms>

Appendix A - Search terms used in the PROMOTION registry

Bladder cancer RCTs

("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR sexual OR functioning) AND bladder

Breast cancer RCTs

("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR sexual OR functioning OR "body image" OR "sexual") AND ("breast" OR "breast cancer" OR "breast carcinoma" OR "breast tumour" OR "breast tumor")

Colorectal + anal cancers RCTs

("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "symptom distress" OR "functional status") AND (colon OR colorectal OR rectum OR rectal OR "hepatic metastases" OR "liver metastases" OR "anal cancer")

Gynaecological cancers RCTs

(gynecological OR GYN OR cervical OR ovarian OR endometrial OR vulvar OR vaginal OR uterine OR hysterectomy OR "fallopian tubes" OR clitoris OR vulva OR vulval OR vaginal OR endometrium OR ovary OR cervix OR uterus OR ovaries OR vagina OR pelvis OR "germ cell" OR genital OR "reproductive system" OR cervical OR "cone biopsy" OR conization OR oophorectomy OR vulvectomy) AND ("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR sexuality OR libido OR "body image" OR arousal OR orgasm OR "sexual desire" OR excitement OR vaginitis OR lubrication OR femininity OR appearance OR intimacy OR intercourse OR relationship OR sexual OR bloating OR sex OR psychosexual OR sexuality OR dyspareunia OR "abdominal swelling" OR constipation OR "vaginal bleeding" OR reconstructive OR "plastic surgery" OR reconstruction) AND (leiomyosarcoma OR sarcoma OR cancer OR malignant OR adenocarcinoma OR malignancy OR carcinoma OR neoplasm OR tumor OR tumour)

Lung cancer RCTs

("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR "pain" OR "fatigue" OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR "sexual" OR "functioning") AND ("lung cancer" OR "lung carcinoma" OR "lung tum" OR "lung" OR "non-small")*

Prostate cancer RCTs

("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR "pain" OR "fatigue" OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR "sexual" OR "functioning") AND prostate

Appendix B

Classification of study endpoints*

Study endpoint	Classified as
Overall survival	Overall survival
Progression-free survival	Progression-free survival
Event-free survival	
Disease-free survival	
Time to progression	
Duration of response	
Toxicity	Toxicity
Safety	
Feasibility	
Maximum-tolerated dose	
Response	Efficacy
Efficacy	
Time to response	
Engraftment	
Time to failure	
Health care utilization	Healthcare utilization
Health economics	
Laboratory parameters	Biological parameters
Genetic parameters	
Tumor biology	
Completion of planned treatment	Completion of treatment
Achieved dose intensity	
Compliance to treatment	

*Based on classification performed by Hamaker et al. *Ann Oncol* 25:675-681, 2014.

Appendix C

References of studies with a high-quality PRO reporting

1. Prescott RJ, Kunkler IH, Williams LJ, et al. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess.* 2007;11(31):1-149, iii-iv.
2. Williams LJ, Kunkler IH, King CC, Jack W, van der Pol M. A randomised controlled trial of post-operative radiotherapy following breast-conserving surgery in a minimum-risk population. Quality of life at 5 years in the PRIME trial. *Health Technol Assess.* 2011;15(12):i-xi, 1-57.
3. Kabbinavar FF, Wallace JF, Holmgren E, et al. Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and leucovorin or 5-fluorouracil and leucovorin for metastatic colorectal cancer. *Oncologist.* 2008;13(9):1021-1029.
4. Price N. Bevacizumab improves the efficacy of 5-fluorouracil/leucovorin in patients with advanced colorectal cancer. *Clin Colorectal Cancer.* 2004;4(2):89-91.
5. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol.* 2005;23(16):3697-3705.
6. van Hooft JE, Bemelman WA, Oldenburg B, et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol.* 2011;12(4):344-352.
7. Janson M, Bjorholt I, Carlsson P, et al. Randomized clinical trial of the costs of open and laparoscopic surgery for colonic cancer. *Br J Surg.* 2004;91(4):409-417.
8. Janson M, Edlund G, Kressner U, et al. Analysis of patient selection and external validity in the Swedish contribution to the COLOR trial. *Surg Endosc.* 2009;23(8):1764-1769.
9. Janson M, Lindholm E, Anderberg B, Haglind E. Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. *Surg Endosc.* 2007;21(5):747-753.
10. Buunen M, Veldkamp R, Hop WC, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol.* 2009;10(1):44-52.
11. Kuhry E, Bonjer HJ, Haglind E, et al. Impact of hospital case volume on short-term outcome after laparoscopic operation for colonic cancer. *Surg Endosc.* 2005;19(5):687-692.
12. Aparicio T, Gargot D, Teillet L, et al. Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderly metastatic colorectal cancer patients. *Eur J Cancer.* 2017;74:98-108.
13. Aparicio T, Jouve JL, Teillet L, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. *J Clin Oncol.* 2013;31(11):1464-1470.
14. Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). *Ann Oncol.* 2016;27(1):121-127.
15. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Analysis of longitudinal quality-of-life data in high-risk operable patients with lung cancer: results from the ACOSOG Z4032 (Alliance) multicenter randomized trial. *J Thorac Cardiovasc Surg.* 2015;149(3):718-725; discussion 725-716.
16. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Impact of brachytherapy on local recurrence rates after sublobar resection: results from ACOSOG Z4032 (Alliance), a phase III randomized trial for high-risk operable non-small-cell lung cancer. *J Clin Oncol.* 2014;32(23):2456-2462.
17. Berry DL, Moinpour CM, Jiang CS, et al. Quality of life and pain in advanced stage prostate cancer: results of a Southwest Oncology Group randomized trial comparing docetaxel and estramustine to mitoxantrone and prednisone. *J Clin Oncol.* 2006;24(18):2828-2835.
18. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351(15):1513-1520.
19. Ahles TA, Herndon JE, 2nd, Small EJ, et al. Quality of life impact of three different doses of suramin in patients with metastatic hormone-refractory prostate carcinoma: results of Intergroup O159/Cancer and Leukemia Group B 9480. *Cancer.* 2004;101(10):2202-2208.

20. Small EJ, Halabi S, Ratain MJ, et al. Randomized study of three different doses of suramin administered with a fixed dosing schedule in patients with advanced prostate cancer: results of intergroup 0159, cancer and leukemia group B 9480. *J Clin Oncol*. 2002;20(16):3369-3375.
21. Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer*. 2005;4(1):31-37.
22. Saad F, Chen YM, Gleason DM, Chin J. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. *Clin Genitourin Cancer*. 2007;5(6):390-396.
23. Saad F, Eastham J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology*. 2010;76(5):1175-1181.
24. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468.
25. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96(11):879-882.
26. Weinfurt KP, Li Y, Castel LD, et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol*. 2005;16(4):579-584.
27. Salonen AJ, Taari K, Ala-Opas M, Viitanen J, Lundstedt S, Tammela TL. Advanced prostate cancer treated with intermittent or continuous androgen deprivation in the randomised FinnProstate Study VII: quality of life and adverse effects. *Eur Urol*. 2013;63(1):111-120.
28. Salonen AJ, Taari K, Ala-Opas M, Viitanen J, Lundstedt S, Tammela TL. The FinnProstate Study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. *J Urol*. 2012;187(6):2074-2081.
29. Salonen AJ, Viitanen J, Lundstedt S, Ala-Opas M, Taari K, Tammela TL. Finnish multicenter study comparing intermittent to continuous androgen deprivation for advanced prostate cancer: interim analysis of prognostic markers affecting initial response to androgen deprivation. *J Urol*. 2008;180(3):915-919; discussion 919-920.
30. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flashes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010;11(2):147-154.
31. Fradet Y, Egerdie B, Andersen M, et al. Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol*. 2007;52(1):106-114.
32. Collette L, de Reijke TM, Schroder FH. Prostate specific antigen: a prognostic marker of survival in good prognosis metastatic prostate cancer? (EORTC 30892). *Eur Urol*. 2003;44(2):182-189; discussion 189.
33. Schroder FH, Collette L, de Reijke TM, Whelan P. Prostate cancer treated by anti-androgens: is sexual function preserved? EORTC Genitourinary Group. European Organization for Research and Treatment of Cancer. *Br J Cancer*. 2000;82(2):283-290.
34. Schroder FH, Whelan P, de Reijke TM, et al. Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) Protocol 30892. *Eur Urol*. 2004;45(4):457-464.
35. Green HJ, Pakenham KI, Headley BC, Gardiner RA. Coping and health-related quality of life in men with prostate cancer randomly assigned to hormonal medication or close monitoring. *Psychooncology*. 2002;11(5):401-414.
36. Green HJ, Pakenham KI, Headley BC, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. *BJU Int*. 2002;90(4):427-432.
37. Green HJ, Pakenham KI, Headley BC, et al. Quality of life compared during pharmacological treatments and clinical monitoring for non-localized prostate cancer: a randomized controlled trial. *BJU Int*. 2004;93(7):975-979.
38. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
39. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive

- patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol.* 2015;16(5):509-521.
40. Devlin N, Herdman M, Pavesi M, et al. Health-related quality of life effects of enzalutamide in patients with metastatic castration-resistant prostate cancer: an in-depth post hoc analysis of EQ-5D data from the PREVAIL trial. *Health Qual Life Outcomes.* 2017;15(1):130.
 41. Bruner DW, Hunt D, Michalski JM, et al. Preliminary patient-reported outcomes analysis of 3-dimensional radiation therapy versus intensity-modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group (RTOG) 0126 prostate cancer trial. *Cancer.* 2015;121(14):2422-2430.
 42. Michalski JM, Yan Y, Watkins-Bruner D, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys.* 2013;87(5):932-938.
 43. Michalski JM, Moughan J, Purdy J, et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. *JAMA Oncol.* 2018;4(6):e180039.
 44. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. *N Engl J Med.* 2013;368(14):1314-1325.
 45. Mason M, Maldonado Pijoan X, Steidle C, et al. Neoadjuvant androgen deprivation therapy for prostate volume reduction, lower urinary tract symptom relief and quality of life improvement in men with intermediate- to high-risk prostate cancer: a randomised non-inferiority trial of degarelix versus goserelin plus bicalutamide. *Clin Oncol (R Coll Radiol).* 2013;25(3):190-196.
 46. Axcrona K, Aaltomaa S, da Silva CM, et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. *BJU Int.* 2012;110(11):1721-1728.
 47. Heidenreich A, Chowdhury S, Klotz L, et al. Impact of Enzalutamide Compared with Bicalutamide on Quality of Life in Men with Metastatic Castration-resistant Prostate Cancer: Additional Analyses from the TERRAIN Randomised Clinical Trial. *Eur Urol.* 2017;71(4):534-542.
 48. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. *Lancet Oncol.* 2016;17(2):153-163.
 49. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol.* 2016;17(6):727-737.
 50. Duchesne GM, Woo HH, King M, et al. Health-related quality of life for immediate versus delayed androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol.* 2017;18(9):1192-1201.
 51. Gilbert DC, Duong T, Kynaston HG, et al. Quality-of-life outcomes from the Prostate Adenocarcinoma: TransCutaneous Hormones (PATCH) trial evaluating luteinising hormone-releasing hormone agonists versus transdermal oestradiol for androgen suppression in advanced prostate cancer. *BJU Int.* 2017;119(5):667-675.
 52. Langley RE, Cafferty FH, Alhasso AA, et al. Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). *Lancet Oncol.* 2013;14(4):306-316.
 53. Langley RE, Kynaston HG, Alhasso AA, et al. A Randomised Comparison Evaluating Changes in Bone Mineral Density in Advanced Prostate Cancer: Luteinising Hormone-releasing Hormone Agonists Versus Transdermal Oestradiol. *Eur Urol.* 2016;69(6):1016-1025.
 54. Annala M, Vandekerckhove G, Khalaf D, et al. Circulating Tumor DNA Genomics Correlate with Resistance to Abiraterone and Enzalutamide in Prostate Cancer. *Cancer Discov.* 2018;8(4):444-457.
 55. Khalaf DJ, Sunderland K, Eigl BJ, et al. Health-related Quality of Life for Abiraterone Plus Prednisone Versus Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer: Results from a Phase II Randomized Trial. *Eur Urol.* 2018.

56. Saad F, Cella D, Basch E, et al. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19(10):1404-1416.
57. Smith MR, Saad F, Chowdhury S, et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med.* 2018;378(15):1408-1418.