Prevalence of erectile dysfunction at different time points in male patients with cancer: a systematic review and meta-analysis of longitudinal studies

Tao Xiao*[1], Damiano Pizzol*[2], Igor Grabovac[3±], Petre Cristian Ilie[4], Lin Yang[5], Yvonne Barnett[6], Christopher Parris[7], Daragh T. McDermott[8], Nicola Veronese[9], Andreas Kronbichler[10], Mike Trott[11], Pinar Soysal[12], Louis Jacob[13,14], Ai Koyanagi[14,15], Jae Il Shin[16], Lee Smith[17]

1. College of Mathematics and Statistics, Shezhen University, Shenzhen, China
2. Italian Agency for Development Cooperation – Khartoum, Sudan
3. Department of Social and Preventive Medicine, Centre for Public Health, Medical University of Vienna, Vienna, Austria
4. Research and Innovation Department, The Queen Elizabeth Hospital Foundation Trust, King's Lynn, UK
5. Department of Cancer Epidemiology and Prevention Research, Cancer Control Alberta, Alberta Health Services, Calgary, AB T2S 3C3, Canada; Departments of Oncology and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB T2N 4N1, Canada
6. Anglia Ruskin University, Cambridge, UK
7. Biomedical Research Group, Faculty of Science and Engineering, Anglia Ruskin University, Cambridge, UK
8. School of Psychology and Sport Science, Anglia Ruskin University, Cambridge CB11PT
9. Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy
10. Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, 6020 Innsbruck, Austria
11. Vision and Eye Research Institute, Anglia Ruskin University, Cambridge, UK
12. Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey
13. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux 78180, France

14. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Barcelona, Spain
15. ICREA, Pg. Lluis Companys 23, Barcelona, Spain
16. Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea.
17.Centre for Health Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK, CB1 1PT

Introduction

Erectile dysfunction (ED), defined as the inability to achieve and/or maintain a sufficient erection to allow satisfactory sexual intercourse [1], is one of the most common sexual dysfunction in men and might result from psychological, neurologic, hormonal, arterial or cavernosal impairment or the combination of these factors [2]. ED is associated with a wide range of physical and psychological adverse health impacts including anxiety, low mood and reductions in personal and couple's quality of life that, in turn, may worsen the sexual function [3]. In particular, ED is reported as one of the most distressing consequences of cancer diagnosis and treatment in men [4], especially in pelvic cancers [5]. Owing to advancing therapeutic options, life expectancy in cancer patients is increasing, and therefore, quality of life, including sexuality, is of increasing importance for this population. Moreover, considering the long-lasting therapies and sequelae, it is of paramount importance to understand the course of sexual functions not just immediately after the treatment but in a long term cancer survivorship. Therefore, longitudinal design studies have been conducted to facilitate follow-up of sexual outcomes among cancer survivors. In this paper, we summarise the study-level longitudinal ED prevalence for cancer patients along different time points and assess the moderator effects on heterogeneity of those study-level prevalence observations.

Material and methods

Search strategy

We searched four electronic databases – Medline, Cinhal, PsychInfo and Embase – targeting reports published until 1st of February 2022. The following search strategy was used: ("erectile dysfunction" OR "erectile function" OR "sexual dysfunction" OR

"sexual function" OR “impotence”) AND (“cancer” OR “solid cancer” OR “neoplasia” OR “tumor” OR “solid tumor” OR “Sarcoma” OR “Carcinoma” OR “Lymphoma” OR “Colon carcinoma” OR “Prostate cancer” OR “Lung cancer” OR “Skin cancer” OR “Liver cancer” OR “Bone cancer” OR “Pancreas cancer” OR “Brain cancer” OR “Head cancer” OR “Neck cancer” OR “Kidney cancer” OR “Renal Cancer” OR “Thyroid cancer” OR “Neuroblastoma” OR “Wilms’ Tumor” OR “Retinoblastoma” OR “Posterior uveal melanoma” OR “Hodgkin OR “Non-Hodgkin ” OR “Rhabdomyosarcoma” OR “Osteogenic Sarcoma” OR “Ewing’s Sarcoma” OR “Angiosarcoma” OR “Chondrosarcoma”).

The references of retrieved articles together with the proceedings of relevant conferences were hand-searched in order to identify other potentially eligible studies for inclusion in the analysis missed by the initial search or any unpublished data.

The literature search, assessment of inclusion and exclusion criteria, quality of studies and extraction of data were independently undertaken and verified by two investigators (TX, DP). The results were then compared and, in case of discrepancies, a consensus was reached with the involvement of a third senior investigator (LS). There was no language restriction.

Type of studies, inclusion and exclusion criteria

All retrospective or prospective studies reporting the prevalence of ED in male patients with cancer and using a validated tool for the detection of ED (e.g. the International Index of Erectile Function, IIEF-5) with at least two measurements. We excluded studies that did not meet the inclusion criteria.

Data extraction and statistical analyses

Statistical analyses based on these data were performed using R (version 3.6.1) [6]. Heterogeneity of these 32 studies across different time points was assessed by the I^2 metric by a random-effects MA model and taking as measure of high heterogeneity if I^2 >50% or p<0.05 for testing the Chi2-distributed Q statistic [6]. In case of high heterogeneity of prevalence of ED at different time points across studies, we conducted meta analyses which were divided into the following two parts: (1) compared odds of ED for male cancer patients at the first observation time after cancer treatment to that at cancer diagnosis time, adjusting for any potential moderators using a manual meta-regression model building procedure; we used logit or log(Odds) transformed ED prevalence (i.e., log[prevalence/(1-prevalence)]) across primary studies to assure that the transformed prevalence satisfies the model assumption of normally distributed dependent variable, while we presented our findings in the scale of odds of ED by exponentiating regression coefficient estimates; (2) summarised prevalence of ED for different cancers at various time points in a table: if there are more than one primary studies available for a cancer (i.e., n>1), a random-effect MA model was used and a forest plot for this cancer categorised by time points was given, otherwise (i.e., n=1), only the prevalence estimate reported by the original primary study was presented for this cancer.

Results

The electronic search yielded 2419 studies that were assessed for inclusion in the review. Of those, 141 were potentially eligible and subsequently scrutinised in full text (Figure 1).

Excluded studies

Amongst the relevant studies, 109 failed to meet the inclusion criteria and were excluded from this review mainly due to the lack of validated tools used to assess

ED, the lack of data on ED prevalence and the non-longitudinal nature of the study.

Included studies, their quantities and overall heterogeneity

The 32 studies included a total of 5,657 participants. The majority of the studies (n=11) were conducted in North America, 9 in Europe, 8 in Asia, 2 in Middle East, 1 in Oceania and 1 in South America. The most affected sites were: prostate (19 studies), rectum (8) and testis, bladder, penis, lung and multiple sites (1 each).

The 32 studies included in the meta-analysis were all longitudinal studies of ED prevalence among cancer patients with ED prevalence data at minimum two time points available, including one observation at cancer diagnosis and one to six observations at various time points during follow-up period after cancer treatment. Some of these time points reported by primary studies are mean values of patient observation time. Contingency table for count of included primary studies cross tabulated by time (in month) and observation sequence during follow-up period is given in Table 1.

The median quality of the studies was 4.9 (range: 3-7), indicating an overall good quality of the studies, according to the NOS.

We found a high degree of overall heterogeneity of ED prevalence of male cancer patients at different time points and across studies: I^2=96%; Q (degree of freedom = 84) = 1874, p<0.0001.

Comparing ED prevalence of male cancer patients at cancer diagnosis and at the first observation time after cancer treatment

The factors “time” and “cancer site” turned out to be significant in both the univariate and multivariate meta regression. The regression coefficient table for the final multi-

variate meta regression model is given in Table 2, with coefficient estimates exponentiated to get odds ratio estimates. The R^2 value is 42% for this meta regression model, meaning that 42% of the between-study heterogeneity was explained by "time" and "cancer site". Reference levels for "time" and "cancer site" are set to be "time points at cancer diagnosis" and "prostate cancer" respectively in the multivariate meta regression model. The exponential of regression coefficient estimates are given in Table 2 to present estimated odds ratio in comparing non-reference levels of "time" and "cancer site" to their reference levels on ED. The significant findings are stated as follows. The odds of study-reported ED at the first observation time after cancer treatment is 2.44 (95% C.I. 1.72 to 3.47) times of that at cancer diagnosis adjusting for other covariates; the odds of study-reported ED for rectum cancer patients is 2.66 (95% C.I. 1.71 to 4.14) times of that for prostate cancer patients adjusting for other covariates; the odds of study-reported ED for bladder cancer patients is 10.22 (95% C.I. 3.83 to 27.28) times of that for prostate cancer patients adjusting for other covariates; the odds of study-reported ED for lung cancer patients is 5.55 (95% C.I. 1.90 to 16.21) times of that for prostate cancer patients adjusting for other covariates; the odds of study-reported ED for multiple cancer patients is 13.30 (95% C.I. 4.00 to 44.29) times of that for prostate cancer patients adjusting for other covariates.

Summarising prevalence of ED at different time points for different male cancer patients

Forest plots of ED prevalence at different time points for prostate (Figure 2) and rectum (Supplementary 1) cancers are given. In Table 3, we synthesised prevalence estimates at different time points for different cancers including those cancers for which we have collected data of only one primary longitudinal study.

Discussion

People living with and beyond cancer is increasing worldwide and this population often undergoes treatment that may have consequences on short or long term quality of life and morbidity [7]. Predominant cancer treatments (i.e. surgery, chemotherapy, or radiation therapy) include different approaches and strategies based on tumour characteristics and patient health status, but in general, all require a recovery period. Besides the treatment, the diagnosis may also strongly impact the psychological health of the patient resulting both in impaired ability of relationship and reaction to the disease [8]. Sexual health and, in particular erectile function, is a bio-psychosocial process that involves the coordination of psychological, endocrine, vascular, and neurological systems and, thus, is one of the most affected aspects in male cancer survivors depending on a wide range of physiological and personal factors [9]. Regardless of the severity, the restoration of erectile and sexual function represents also a key element in returning to normality after cancer care. As expected, we found an overall high heterogeneity of study reports for prevalence of ED of cancer patients (I-square =96%). It reflects the wide range of factors that could affect erection including psychological components, treatment types, cancer sites and the general health status. We found that "having cancer treatment or not" is an important factor to explain the overall heterogeneity: the mean of reported prevalence/odds of ED for cancer patients at diagnosis is significantly lower than that at the first observation time after treatment adjusting for covariates. This means that cancer treatment would increase the probability of ED for cancer patients. It is well known that operative procedures directly affect sexual function especially in prostate cancer, where the incidence of post-operative ED ranged from 14% to 90%, although with robotic techniques, the reported incidence is lower, ranging from 7% to 33% [10]. Moreover, also the impact of radiotherapy has been described with a reported incidence of ED of

34% at 1 year and 57% at 5.5 years, regardless of the mode of radiation delivery (external beam, brachytherapy or both) [11]. However, despite this in a study of 41 physicians working in the field of radiation oncology only 4.9% of the participants reported routinely exploring sexual health issues in 61–80% of their patients. Thirty-one point seven percent of the doctors suspected sexual problems in about half of their patients but did not raise the issue [12].

We found that "cancer site" is another factor that contributes to the within-stage heterogeneity significantly. That means patients with different cancer sites tend to have different probability of ED (e.g., compared with patients with cancer site "prostate", patients with cancer sites "rectum", "bladder" and "lung" and "multiple" have significantly higher probability of ED). In addition, context and personal factors should be considered. First of all, the importance of the role of the partner has to be taken into account [13]. In fact, often, the diagnosis of cancer changes the partnership dynamics and for this reason, the attention of health workers should be focused on the couple more than the individual cancer survivors. Moreover, the threat of disease recurrence, early death, and bodily disfigurement, as well as economic, employment, and insurance concerns, play a crucial role on the well being of the male cancer patient [14] and, thus, it is essential to consider psychological aspects and take care of them also. At the very least, these aspects should be addressed by physicians for men without partners in order to not hinder the possibility of starting a relationship.

The therapeutic armamentarium for cancer survivors with ED is similar and follows the same treatment algorithm as for patients with ED in general. Commonly after radical prostatectomy, penile rehabilitation is offered as part of post-operative recovery. However, not the same can be said regarding the other types of cancer

surgery. After assessing the cardiovascular risk, addressing the lifestyle changes and risk factor modifications, the initial approach to treating ED can be made with oral therapy (PDE5Is). If that fails, alternative options, vacuum devices, topical/intraurethral Alprostadil and intracavernosal injection with Alprostadil should be discussed with the patients. If none of the above is successful after reassuring adequate use, re-trial and combinations, a penile prosthesis can be discussed with the cancer survivor in selected cases.

Limitations of our analysis include the inherent limitations from the included studies. Due to the small number of primary studies that provide complete clinical and biological (e.g. serum testosterone or estradiol levels) features of the participants, we were not able to run some meta-regression analyses using well-known independent risk factors for ED (such as dyslipidemia, hypertension, diabetes mellitus and depression) as moderators of our findings.

Conclusion

We found that the overall heterogeneity of study reports for prevalence of ED of cancer patients is high. We found that "have cancer treatment or not" is an important factor to explain the overall heterogeneity: the mean of prevalence/odds of ED for cancer patients at diagnosis is significantly lower than that at first observation time after treatment adjusting for covariates. This means that cancer treatment would increase the probability of ED for cancer patients. We also found that "Cancer Site" is a factor that contributes to the overall heterogeneity significantly adjusting for covariates. That means patients with different cancer sites tend to have different probability of ED.

Compliance with Ethical Standards:

Funding: None to declare.

Conflict of Interest: All author declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References

1) NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA. 1993 Jul 7;270(1):83-90.
2) Pizzol D, Xiao T, Yang L, Demurtas J, McDermott D, Garolla A, Nardelotto A, Grabovac I, Soysal P, Kazancioglu RT, Veronese N, Smith L. Prevalence of erectile dysfunction in patients with chronic kidney disease: a systematic review and meta-analysis. Int J Impot Res. 2021 Jul;33(5):508-515.
3) Lizza EF, Rosen RC. Definition and classification of erectile dysfunction: report of the Nomenclature Committee of the International Society of Impotence Research. Int J Impot Res. 1999 Jun;11(3):141-3.
4) Virag R, Zwang G, Dermange H, Legman M. Vasculogenic impotence: a review of 92 cases with 54 surgical operations. Vasc Surg. 1981;15:9–17.
5) Gettman MT, Blute ML. Critical comparison of laparoscopic, robotic and open radical prostatectomy: Techniques, outcomes, and cost. Curr Urol Rep 2006;7:193–9.
6) R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/
7) Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statis- tics, 2019. CA Cancer J Clin. 2019;69:363–385.
8) Sun V, Grant M, Wendel CS, et al. Sexual function and health-related quality of life in long-term rectal cancer survivors. J Sex Med. 2016;13:1071–1079.
9) Pizzol D, Smith L, Fontana L, Caruso MG, Bertoldo A, Demurtas J, McDermott D, Garolla A, Grabovac I, Veronese N. Associations between body mass index,

waist circumference and erectile dysfunction: a systematic review and META-analysis. Rev Endocr Metab Disord. 2020 Dec;21(4):657-666.

10) Attaallah W, Ertekin SC, Yegen C. Prospective study of sexual dysfunction after proctectomy for rectal cancer. Asian J Surg. 2018;41:454–461.

11) Gaither TW, Awad MA, Osterberg EC, et al. The natural history of erectile dysfunc- tion after prostatic radiotherapy: a systematic review and meta-analysis. J Sex Med. 2017;14:1071–1078.

12) Bräutigam E, Schratter-Sehn A, Kottmel A, Bitzer J, Teleky B, Ucsnik L. Do radiation oncologists talk about sexual health and dysfunction with their cancer patients? Results of the igls-vienna-sexmed-survey. *Clin Transl Radiat Oncol*. 2020;21:120-126. Published 2020 Jan 31. doi:10.1016/j.ctro.2020.01.005

13) Soloway CT, Soloway MS, Kim SS, Kava BR. Sexual, psychological and dyadic quali- ties of the prostate cancer 'couple'. BJU Int. 2005;5:780–785.

14) Falk SJ, Dizon DS. Sexual Health Issues in Cancer Survivors. Semin Oncol Nurs. 2020;36(1):150981.

Figures legend

Figure 1: PRISMA flow-chart

Figure 2: Forest plot for prevalence of ED for prostate cancer.

Supplementary 1: Forest plot for prevalence of ED for rectum cancer.

Supplementary 1 continued: Forest plot for prevalence of ED for rectum cancer.

Table 1: Contingency table for count of included primary studies cross tabulated by time (in month) and observation sequence during follow-up period

	Observation sequence					
Follow-up month	1st obs.	2nd obs.	3rd obs.	4th obs.	5th obs.	6th obs.
0	1	0	0	0	0	0
3	1	0	0	0	0	0
6	6	0	0	0	0	0
12	9	6	0	0	0	0
18	0	0	1	0	0	0
21	1	0	0	0	0	0
23.5(mean)	1	0	0	0	0	0
24	5	0	3	1	0	0
36	1	0	0	1	0	0
36.8(mean)	1	0	0	0	0	0
48	0	0	0	1	2	0
60	1	2	0	0	1	1
69	1	0	0	0	0	0
96	0	0	0	0	0	1
116.58(mean)	1	0	0	0	0	0
Missing	3	1	0	0	0	0
Total	32	9	4	3	3	2

Table 2: Regression coefficient table for multivariate meta regression analysis

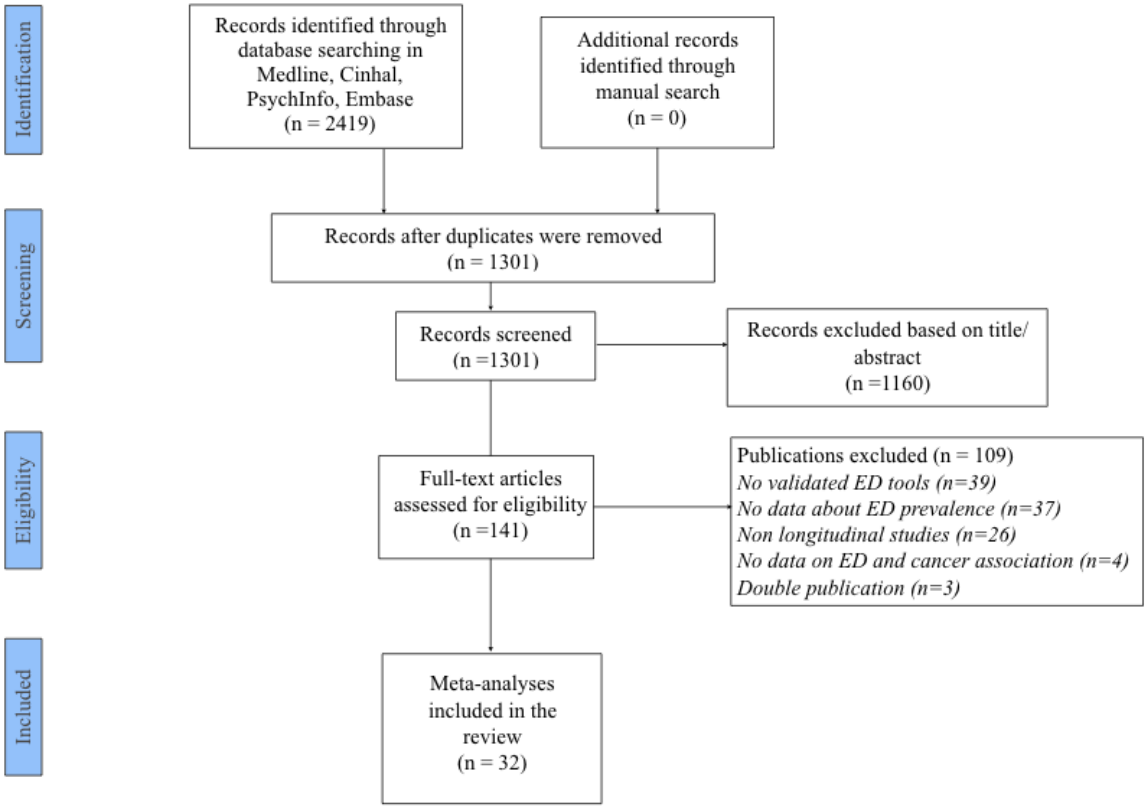
Regression Coefficient	Level	Exponential of coefficient estimate	95% C.I.	P-value
		0.5758122	(0.43619402, 0.7601198)	<.0001 ***
Time	1st obs. time after treatment	2.4412359	(1.71787074, 3.4691974)	<.0001 ***
Cancer site	Rectum	2.6621536	(1.71252269, 4.1383753)	<.0001 ***
	Bladder	10.2237684	(3.83125024, 27.2823319)	<.0001 ***
	Lung	5.5517395	(1.90169727, 16.2075276)	0.0017 **
	Penis	0.3403083	(0.08236183, 1.4061094)	0.1365
	Testis	0.5644353	(0.21581969, 1.4761728)	0.2436
	Multiple	13.3038150	(3.99599873, 44.2921796)	<.0001 ***

Table 3: Estimated prevalence of ED at different time points for different male cancer patients

		Prostate	Rectum	Bladder	Lung	Penis	Testis	Multiple
At diagnosis		0.3667 (0.3108,0.4264), n=19	0.6122 (0.3376,0.8302), n=8	0.8571 (0.8009, 0.8995), n=1	0.7400 (0.6021, 0.8426), n=1	0.0263 (0.0016,0.3096), n=1	0.3776 (0.3186,0.4404), n=1	0.9375 (0.8234,0.9797), n=1
	0							0.9111 (0.7859,0.9662), n=1
	3		0.7959 (0.6607, 0.8865), n=1					
	6	0.5100 (0.3599,0.6582), n=3	0.9829 (0.9342, 0.9957), n=1		0.9000 (0.6021, 0.8426), n=1		0.2838 (0.1929, 0.3964), n=1	
	12	0.5548 (0.4617,0.6442), n=9	0.7957 (0.4759,0.9435), n=4				0.2364 (0.1662, 0.3246), n=1	0.9778 (0.8584,0.9969), n=1
	18						0.1833 (0.1045, 0.3015), n=1	

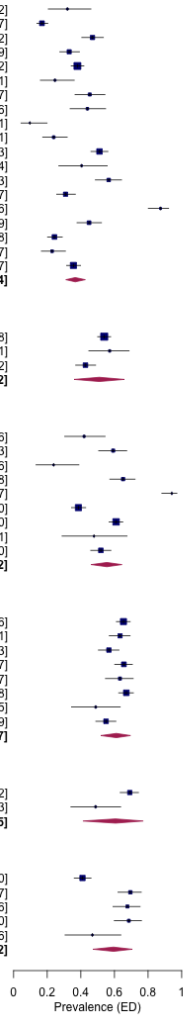
	21		0.7674 (0.6193, 0.8701) , n=1					
	23.5					0.4444 (0.2400,0.6696), n=1		
	24	0.6110 (0.5191,0.6957), n=8					0.1600 (0.0932, 0.2610), n=1	
	36	0.3830 (0.1609, 0.6677), n=1	0.8214 (0.6362, 0.9237), n=1					
	36.80	0.7500 (0.5741,0.8698), n=1						
	48	0.6061 (0.4122,0.7715), n=2					0.2537 (0.1640, 0.3709), n=1	
	60	0.5944 (0.4731,0.7052), n=5						
	69	0.5897 (0.4986, 0.6751), n=1						

	96						0.3056 (0.1780, 0.4721), n=1	
	116.58	0.6591 (0.5860, 0.7253), n=1						
	Unknown time 1	0.6304 (04839, 0.7564), n=1	0.5455 (0.4469,0.6406), n=1	0.9337 (0.8891, 0.9611), n=1				
	Unknown time 2	0.8214 (0.6362,,0.9237), n=1						

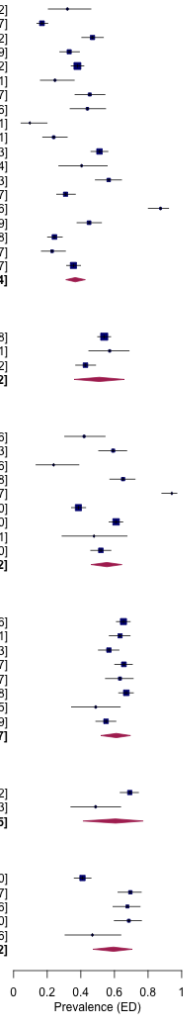
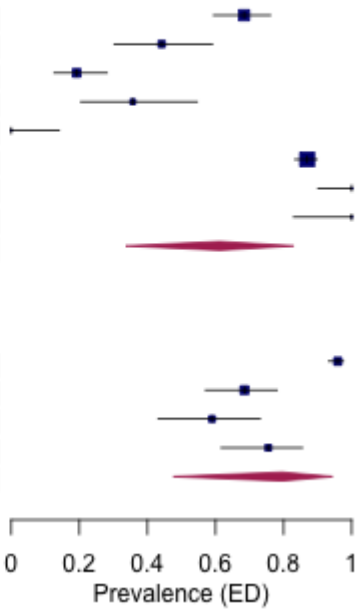


Supplementary figure 1. PRISMA flow-chart.

Study	Proportion	95% C.I.
time_point = (a) At diagnosis		
al-Abany, 2000	0.3200	[0.2062; 0.4602]
Alemozaffar-1, 2011	0.1686	[0.1386; 0.2037]
Alemozaffar-2, 2011	0.4693	[0.4054; 0.5342]
Alemozaffar-3, 2011	0.3306	[0.2746; 0.3919]
Bazinet, 2019	0.3796	[0.3424; 0.4182]
Brown, 2006	0.2464	[0.1590; 0.3611]
Chasseray, 2019	0.4530	[0.3653; 0.5437]
Chelly, 2020	0.4390	[0.3360; 0.5476]
Cozzarini, 2016	0.0968	[0.0441; 0.1991]
Davison, 2007	0.2385	[0.1730; 0.3191]
Dess, 2017	0.5108	[0.4600; 0.5613]
Fujioka, 2004	0.4048	[0.2686; 0.5574]
Fujita, 2009	0.5658	[0.4860; 0.6423]
Hoppe, 2012	0.3092	[0.2562; 0.3677]
Matsushima, 2013	0.8739	[0.8014; 0.9226]
Morgia, 2015	0.4489	[0.3770; 0.5229]
Ong, 2014	0.2432	[0.2019; 0.2898]
Spratt, 2017	0.2290	[0.1650; 0.3087]
Woo, 2014	0.3559	[0.3152; 0.3987]
Random effects model	**0.3667**	**[0.3108; 0.4264]**
Heterogeneity: I^2 = 94%, τ^2 = 0.2690, χ^2_{18} = 306 (p < 0.01)		
time_point = (b) 6 months after treatment		
Bazinet, 2019	0.5391	[0.4999; 0.5778]
Chelly, 2020	0.5714	[0.4474; 0.6871]
Hoppe, 2012	0.4275	[0.3689; 0.4882]
Random effects model	**0.5100**	**[0.3599; 0.6582]**
Heterogeneity: I^2 = 80%, τ^2 = 0.2690, χ^2_{2} = 10 (p < 0.01)		
time_point = (c) 12 months after treatment		
Cozzarini, 2016	0.4194	[0.3037; 0.5446]
Davison, 2007	0.5923	[0.5059; 0.6733]
Fujioka, 2004	0.2381	[0.1332; 0.3886]
Fujita, 2009	0.6513	[0.5723; 0.7228]
Matsushima, 2013	0.9412	[0.8817; 0.9717]
Woo, 2014	0.3857	[0.3441; 0.4290]
Bazinet, 2019	0.6097	[0.5678; 0.6500]
Chelly, 2020	0.4783	[0.2880; 0.6751]
Hoppe, 2012	0.5191	[0.4586; 0.5790]
Random effects model	**0.5548**	**[0.4617; 0.6442]**
Heterogeneity: I^2 = 94%, τ^2 = 0.2690, χ^2_{8} = 127 (p < 0.01)		
time_point = (d) 24 months after treatment		
Alemozaffar-1, 2011	0.6536	[0.6113; 0.6936]
Alemozaffar-2, 2011	0.6332	[0.5689; 0.6931]
Alemozaffar-3, 2011	0.5668	[0.5043; 0.6273]
Dess, 2017	0.6559	[0.6014; 0.7067]
Spratt, 2017	0.6328	[0.5461; 0.7117]
Bazinet, 2019	0.6705	[0.6251; 0.7128]
Chelly, 2020	0.4884	[0.3442; 0.6345]
Hoppe, 2012	0.5496	[0.4889; 0.6089]
Random effects model	**0.6110**	**[0.5191; 0.6957]**
Heterogeneity: I^2 = 65%, τ^2 = 0.2690, χ^2_{7} = 20 (p < 0.01)		
time_point = (e) 48 months after treatment		
Bazinet, 2019	0.6912	[0.6338; 0.7432]
Chelly, 2020	0.4878	[0.3405; 0.6373]
Random effects model	**0.6061**	**[0.4122; 0.7715]**
Heterogeneity: I^2 = 84%, τ^2 = 0.2690, χ^2_{1} = 6 (p = 0.01)		
time_point = (f) 60 months after treatment		
Ong, 2014	0.4098	[0.3606; 0.4610]
Dess, 2017	0.6946	[0.6207; 0.7597]
Spratt, 2017	0.6772	[0.5912; 0.7526]
Bazinet, 2019	0.6855	[0.5987; 0.7610]
Chelly, 2020	0.4688	[0.3059; 0.6386]
Random effects model	**0.5944**	**[0.4731; 0.7052]**
Heterogeneity: I^2 = 93%, τ^2 = 0.2690, χ^2_{4} = 60 (p < 0.01)		
Heterogeneity: I^2 = 95%, τ^2 = 0.2690, χ^2_{45} = 982 (p < 0.01)		



Study	Proportion	95% C.I.
time_point = (a) At diagnosis		
al-Abany, 2000	0.3200	[0.2062; 0.4602]
Alemozaffar-1, 2011	0.1686	[0.1386; 0.2037]
Alemozaffar-2, 2011	0.4693	[0.4054; 0.5342]
Alemozaffar-3, 2011	0.3306	[0.2746; 0.3919]
Bazinet, 2019	0.3796	[0.3424; 0.4182]
Brown, 2006	0.2464	[0.1590; 0.3611]
Chasseray, 2019	0.4530	[0.3653; 0.5437]
Chelly, 2020	0.4390	[0.3360; 0.5476]
Cozzarini, 2016	0.0968	[0.0441; 0.1991]
Davison, 2007	0.2385	[0.1730; 0.3191]
Dess, 2017	0.5108	[0.4600; 0.5613]
Fujioka, 2004	0.4048	[0.2686; 0.5574]
Fujita, 2009	0.5658	[0.4860; 0.6423]
Hoppe, 2012	0.3092	[0.2562; 0.3677]
Matsushima, 2013	0.8739	[0.8014; 0.9226]
Morgia, 2015	0.4489	[0.3770; 0.5229]
Ong, 2014	0.2432	[0.2019; 0.2898]
Spratt, 2017	0.2290	[0.1650; 0.3087]
Woo, 2014	0.3559	[0.3152; 0.3987]
Random effects model	**0.3667**	**[0.3108; 0.4264]**
Heterogeneity: I^2 = 94%, τ^2 = 0.2690, χ^2_{18} = 306 (p < 0.01)		
time_point = (b) 6 months after treatment		
Bazinet, 2019	0.5391	[0.4999; 0.5778]
Chelly, 2020	0.5714	[0.4474; 0.6871]
Hoppe, 2012	0.4275	[0.3689; 0.4882]
Random effects model	**0.5100**	**[0.3599; 0.6582]**
Heterogeneity: I^2 = 80%, τ^2 = 0.2690, χ^2_{2} = 10 (p < 0.01)		
time_point = (c) 12 months after treatment		
Cozzarini, 2016	0.4194	[0.3037; 0.5446]
Davison, 2007	0.5923	[0.5059; 0.6733]
Fujioka, 2004	0.2381	[0.1332; 0.3886]
Fujita, 2009	0.6513	[0.5723; 0.7228]
Matsushima, 2013	0.9412	[0.8817; 0.9717]
Woo, 2014	0.3857	[0.3441; 0.4290]
Bazinet, 2019	0.6097	[0.5678; 0.6500]
Chelly, 2020	0.4783	[0.2880; 0.6751]
Hoppe, 2012	0.5191	[0.4586; 0.5790]
Random effects model	**0.5548**	**[0.4617; 0.6442]**
Heterogeneity: I^2 = 94%, τ^2 = 0.2690, χ^2_{8} = 127 (p < 0.01)		
time_point = (d) 24 months after treatment		
Alemozaffar-1, 2011	0.6536	[0.6113; 0.6936]
Alemozaffar-2, 2011	0.6332	[0.5689; 0.6931]
Alemozaffar-3, 2011	0.5668	[0.5043; 0.6273]
Dess, 2017	0.6559	[0.6014; 0.7067]
Spratt, 2017	0.6328	[0.5461; 0.7117]
Bazinet, 2019	0.6705	[0.6251; 0.7128]
Chelly, 2020	0.4884	[0.3442; 0.6345]
Hoppe, 2012	0.5496	[0.4889; 0.6089]
Random effects model	**0.6110**	**[0.5191; 0.6957]**
Heterogeneity: I^2 = 65%, τ^2 = 0.2690, χ^2_{7} = 20 (p < 0.01)		
time_point = (e) 48 months after treatment		
Bazinet, 2019	0.6912	[0.6338; 0.7432]
Chelly, 2020	0.4878	[0.3405; 0.6373]
Random effects model	**0.6061**	**[0.4122; 0.7715]**
Heterogeneity: I^2 = 84%, τ^2 = 0.2690, χ^2_{1} = 6 (p = 0.01)		
time_point = (f) 60 months after treatment		
Ong, 2014	0.4098	[0.3606; 0.4610]
Dess, 2017	0.6946	[0.6207; 0.7597]
Spratt, 2017	0.6772	[0.5912; 0.7526]
Bazinet, 2019	0.6855	[0.5987; 0.7610]
Chelly, 2020	0.4688	[0.3059; 0.6386]
Random effects model	**0.5944**	**[0.4731; 0.7052]**
Heterogeneity: I^2 = 93%, τ^2 = 0.2690, χ^2_{4} = 60 (p < 0.01)		
Heterogeneity: I^2 = 95%, τ^2 = 0.2690, χ^2_{45} = 982 (p < 0.01)		



Study	Proportion	95% C.I.
time_point = (a) At diagnosis		
Attaallah, 2018	0.6838	[0.5942; 0.7615]
Costa, 2018	0.4419	[0.3025; 0.5910]
Hendren, 2005	0.1919	[0.1259; 0.2814]
Lee, 2010	0.3571	[0.2041; 0.5462]
Nishizawa, 2011	0.0000	[0.0006; 0.1407]
Saito, 2016	0.8692	[0.8332; 0.8985]
Song-1, 2010	1.0000	[0.9011; 0.9996]
Song-2, 2010	1.0000	[0.8292; 0.9992]
Random effects model	**0.6122**	**[0.3376; 0.8302]**
Heterogeneity: I^2 = 96%, τ^2 = 2.1180, χ^2_{7} = 186 (p < 0.01)		
time_point = (b) 12 months after treatment		
Saito, 2016	0.9592	[0.9323; 0.9757]
Song-1, 2010	0.6849	[0.5702; 0.7808]
Song-2, 2010	0.5897	[0.4316; 0.7312]
Nishizawa, 2011	0.7551	[0.6165; 0.8553]
Random effects model	**0.7957**	**[0.4759; 0.9435]**
Heterogeneity: I^2 = 95%, τ^2 = 2.1180, χ^2_{3} = 58 (p < 0.01)		
Heterogeneity: I^2 = 96%, τ^2 = 2.1180, χ^2_{11} = 259 (p < 0.01)