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Citation for final published version:

Mainwaring, A., Bullock, N., Ellul, T., Hughes, O. and Featherstone, J. 2020. The top 100 most cited manuscripts in bladder cancer: A bibliometric analysis (review article). *International Journal of Surgery* 75 , pp. 130-138. 10.1016/j.ijssu.2020.01.128

Publishers page: <http://dx.doi.org/10.1016/j.ijssu.2020.01.128>

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## **The top 100 most cited manuscripts in bladder cancer**

### **Abstract**

#### **Background:**

Bladder cancer is one of the top 10 frequently occurring neoplasms worldwide and is responsible for over 150,000 deaths per annum. Bibliometric analysis helps further our knowledge of bladder cancer research, topics and trends. It is useful to identify the most influential articles and its impact pertinent to this field that has helped mould our understanding and management of bladder cancer.

#### **Materials and methods:**

Search terms related to bladder cancer were compiled and used to interrogate the Thompson Reuters Web of Science indexing database. The 100 most cited manuscripts in the English language were identified and further evaluated by theme, manuscript type, journal, year of publication, author and institution.

#### **Results:**

The Web of Science search returned a total of 47,381 manuscripts. The median number of citations among the top 100 was 515, ranging from 2257 to 352. The greatest number of manuscripts in the top 100 were published in the Journal of Urology (n=15), followed by the Journal of Clinical Oncology (n=14) and European Urology (n=13). The most cited paper (Stein et al., Journal of Clinical Oncology 2001, 2257 citations) reported on the long term outcomes from a large cohort of patients that underwent radical cystectomy and bilateral pelvic lymphadenectomy for transitional cell carcinoma. The most prevalent theme was the pathobiology of bladder cancer (n=37) followed by oncological treatment (n=17). The majority of manuscripts were of original research (n=79) mainly based on basic science study design and published from institutions in the USA.

#### **Conclusion:**

The pathobiology and oncological treatment of bladder cancer were the areas with most citations within the top 100. This bibliometric analysis has identified influential articles in the

field on bladder cancer, which provides a useful guide to authors as to what type of article constitutes a highly citable publication in this subject.

Keywords: Bladder cancer; citations; bibliometric analysis

Conflict of interest: None declared.

## **1. Introduction**

Prior to the 19<sup>th</sup> century, reports of bladder tumours had emerged but only until 1830 bladder cancer was truly defined and classified by Francois Chopart of Paris in which he published his findings of bladder tumours from post mortem studies [1]. Bladder cancer in the present day is a recognised common urological malignancy. In 2012, it was reported as the 9<sup>th</sup> commonest malignancy globally, accounting for approximately 430,000 new bladder cancer cases and 165,000 bladder cancer deaths [2]. Bladder cancer management can consume a sizeable proportion of the urologist's and uro-oncologist's workload. During the last few decades, a plethora of bladder cancer papers have been published, however, identifying key and pivotal articles can be challenging amongst the ever-expanding literature.

A citation is received when another peer-reviewed article references a publication. Hence, a citation rank refers to a list of published work that has the most intellectual influence [3]. A citation analysis, also known as a bibliometric analysis, can be used to gauge and rank an article or a journal determined by the frequency of citations it receives, and rank journals by order of impact [4]. Over the years, several medical and surgical disciplines have used citation analysis to identify the most influential papers and journals in their respective field, which include emergency medicine [5], orthopaedic surgery [6], general surgery [3, 7], otolaryngology [8], and oncology [9]. A small number of bibliometric analyses have been published in the field of urology, including andrology [10] and urological emergencies [11], but none have specifically focussed on bladder cancer. The aim of this bibliometric analysis was to identify key topics and research themes together with the most eminent and influential articles that have helped shaped our knowledge and understanding of bladder cancer and its management to date.

## **2. Materials and methods**

The Thompson Reuters Web of Science citation indexing database was interrogated using the method previously published [3, 10]. As the pathobiology and clinical management of bladder cancer is of relevance to several scientific and medical disciplines, it is likely that influential articles concerning relevant topics have been published in a range of journals, not just those

specific to urology. The appropriate search terms were therefore compiled and combined to ensure that all relevant manuscripts were identified, as follows: 'bladder cancer', or 'bladder carcinoma' or 'bladder tumour' or 'urothelial cancer', or 'urothelial carcinoma', or 'urothelial tumour', or 'transitional cell cancer', or 'transitional cell carcinoma' or 'transitional cell tumour'.

Final interrogation of the database was performed independently by two assessors (AM and NB). Results were limited to English language and ranked by citation number, with the top 100 most cited manuscripts further assessed according to manuscript type, theme, authorship, journal and year of publication, institution and country of origin. Articles were excluded if, following independent assessment, it was agreed the main focus was not directly relevant bladder cancer. The 2018 impact factor of each journal of publication was identified using the Journal Citation Reports dataset [12]. An additional metric, termed citation rate, was calculated by dividing the number of citations by the number of years since publication. This has been described previously and validated as a means of adjusting for bias arising from older manuscripts accruing a higher number of citations over time [3, 10, 13, 14].

### **3. Results**

The Web of Science search was performed on 15 August 2019 and returned a total of 47,381 manuscripts. Table 1 lists the 100 most cited articles as ranked by citation number, following application of exclusion criteria. In cases where two or more articles had the same number of citations, further stratification was based on citation rate. The median number of citations for a manuscript was 515, ranging from 2257 to 352. The most cited manuscript, with a total of 2257 citations, was that by Stein et al. [15] reporting the long term outcomes from a cohort of 1054 patients that underwent radical cystectomy and bilateral pelvic lymphadenectomy for transitional cell carcinoma between 1971 and 1997, published in the Journal of Clinical Oncology in 2001.

The top 100 most cited manuscripts were published across a range of decades, with numbers increasing from 1970 onwards to a peak between 2000 and 2009 (n=33), as demonstrated in

Figure 1. The most historic paper was that by Jewett and Strong describing the relationship between depth of bladder wall penetration of tumours acquired at autopsy and the presence of metastasis, lymphatic capillary invasion and perivesical fixation, published in the Journal of Urology in 1946 and cited 464 times [16]. The most contemporary manuscripts were those by Bellmunt et al., Babjuk et al. and Sharma et al., all of which were published in March 2017 [17-19].

The journal titles in which the top 100 manuscripts were published are given in Table 2. The greatest number were published in the Journal of Urology, which had a 2018 impact factor of 5.647 (n=15), followed closely by the Journal of Clinical Oncology (n=14; 2018 impact factor of 28.245) and European Urology (n=13; 2018 impact factor of 17.298). The journal with the highest 2018 impact factor was the New England Journal of Medicine, in which 8 of the top 100 manuscripts were published.

The country with the highest number of manuscripts in the top 100 demonstrated in Figure 4 was the United States (n=58), followed by the United Kingdom (n=11) and both Belgium and the Czech Republic (n=5). A number of institutions had more than one manuscript in the top 100, with the greatest number being published by corresponding authors affiliated with the Memorial Sloan-Kettering Cancer Centre, New York, USA (n=11). M Babjuk [18, 20-22] and CN Sternberg [23-26] were the individuals with the most first author publications within the top 100 (n=4 respectively), whilst a number of senior authors achieved two or more.

The distribution of manuscripts according to type is demonstrated in Figure 2A. Most were original articles (n=79), of which 34 (43%) report findings of basic or translational scientific work, 23 (29%) report interventional clinical studies (i.e. clinical trials) and the remaining 22 (28%) report observational clinical studies (Figure 2B). The number of manuscripts relating to each theme within the topic of bladder cancer as a whole are given in Figure 3. The majority focussed on the pathobiology of the disease (n=37), followed by oncological treatment (n=17) and multimodal treatment (n=12) respectively.

The citation rate of the top 100 manuscripts ranged from 6.4 to 399.7, with the top 10 listed in Table 3. Whilst 4 manuscripts ranked in both the top 10 according to total citation number

and citation rate, several were replaced with highly cited more contemporary studies. The most significant change affected the paper by Antoni et al describing the global epidemiology of bladder cancer, published in *European Urology* in 2017, which rose from a rank of 80th according to total citation number (405) to 7th according to citation rate (202.5) [2].

#### **4. Discussion**

This bibliometric analysis is the first study to highlight and decipher the 100 most cited and influential articles within the field of bladder cancer. The highest cited article (2257 citations) was by Stein et al. [15] This original research article, published in the *Journal of Clinical Oncology* in 2001, assessed the long-term results of patients treated with radical cystectomy and pelvic lymph node dissection for invasive bladder cancer. It concluded that radical cystectomy provided good survival results with excellent local recurrence rates for invasive bladder cancer over an extended period of time, therefore advocating aggressive surgical management for invasive bladder cancer. The second highest cited article (n= 1407), a meta-analysis by Sylvester et al.[27] in 2006, evaluated seven European Organisation for Research and Treatment of Cancer (EORTC) trials to predict the risk of cancer recurrence and progression in individual patients with non-muscle invasive bladder cancer. This analysis aided urologists to counsel patients for the most suitable treatment options according to their individual risk of bladder cancer recurrence and progression. Only one other article (n=354) ranked 98<sup>th</sup> within the top 100 cited articles, specifically reports on risk of recurrence and progression for non-muscle invasive bladder cancer [28].

Although a range of themes were identified in our analysis, the majority of articles (n= 37) focussed on the pathobiology of bladder cancer. The article *Comprehensive molecular characterization of urothelial bladder carcinoma* by Weinstein et al. [29] published in the journal *Nature* in 2014 with 1281 citations had the highest number of citations (ranked 4<sup>th</sup>) for a pathobiology themed article. The manuscript was an original research article reporting on the findings from The Cancer Genome Atlas project of the integrated analysis of 131 urothelial carcinomas and their genomic mapping. The study identified statistically significant recurrent mutations in 32 genes, including many genes involved in cell cycle regulation, kinase

signalling pathways and chromatin regulation, together with the identification of 9 genes not previously described as significantly mutated in any cancer. It also highlighted the potential of targeting cellular pathways such as PI3K/AKT/mTOR and RTK/MAPK and mutated chromatin regulatory genes for the treatment for tumours, supporting the paradigm shift from a 'one treatment treats all' approach to a more prescriptive, targeted therapy according to individual tumour genomics.

The topic of oncological treatment (n=17) for bladder cancer, had the second highest number of citations by theme. The original research article by Powles et al. [30] published in the journal *Nature* in 2014 and ranked 5<sup>th</sup> in our analysis, had the highest number of citations (n=1233) for an oncological treatment themed article. This was the first study to assess the effect of anti-PD-L1 antibody MPDL3280A for the treatment of metastatic urothelial bladder cancer (UBC). It showed that tumours expressing PD-L1-positive tumour-infiltrating immune cells had high response rates to the drug and may be better tolerated in patients with renal insufficiency compared to chemotherapy. MPDL3280A may harbour a key role in UBC therapy, hence the drug was bestowed a breakthrough designation status by the USA Food and Drug Administration (FDA) in 2014. Prior to this study, the effects of anti-PD-L1 antibody had been evaluated in patients with advanced melanoma, non-small cell lung cancer, castration-resistant prostate cancer or renal-cell carcinoma [31]. Interestingly, of the three treatment modalities: oncological, surgery and multimodal; surgery themed articles had the fewest number of articles yet had the highest cited article (2257 citations) by Stein et al. [15]. This highlights that the focus of bladder cancer interest is mainly in the pathobiology and oncological treatment of the disease, although it may also reflect some of the challenges associated with conducting high quality, and therefore highly citable, surgical trials. Most of the manuscripts were of original research (n=79) (Figure 2A) and the majority of these (43%) were based on basic science (Figure 2B).

The article with the highest citation rate (399.7) and ranked 8<sup>th</sup> in the top 100 list was by Rosenberg et al. [32] published in 2016 (Table 3). This study reported on the single arm, phase 2 trial evaluating the effects of Atezolizumab, a monoclonal immunoglobulin-G1 antibody that selectively binds to PD-L1, in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy. It



was the first report to demonstrate the association of The Cancer Genome Atlas (TCGA) subtypes with response to immune checkpoint inhibition. Four other articles within the top 10 bladder cancer citation rate list were based on immunotherapy treatment of bladder cancer. The high citation rate of these articles reflects the recent advances in genetics and molecular biology and the shift in interest towards immunotherapy as a treatment for various cancers, compared to traditional strategies.

The highest number of articles within the top 100 were from the USA (n=58), followed by the UK (n=11), Belgium (n= 5) and Czech Republic (n=5). Fifty four of the 58 (93%) articles originating from the USA were original articles, accounting for 68% of all original research articles within the top 100 cited articles. This dominance of academic activity from the USA is not new and has been observed in other bibliometric analyses, such as esophageal cancer [33] and robotic surgery research in urology [34]. The hive of academic activity in the USA has been attributed to higher levels of funding towards academic work compared to other countries, resulting in higher quality of research [10]. Similar to the USA, 10 out of 11 UK articles (91%) were original research articles, mirroring the USA academic attention on original research, only on a smaller scale. Four out of 5 Belgian articles were meta-analyses, all from the EORTC based in Brussels, Belgium. The majority of articles from the Czech Republic (4 out of 5) were the European Association of Urology Guidelines for the management of non-muscle invasive urothelial bladder carcinoma, written by the same first author.

The term 'impact factor' represents the average number of citations of manuscripts pertaining to a journal within a given time period. The Journal of Urology had the highest number of manuscripts in the top 100 (n=15) with a 2018 impact factor of 5.647 and 8171 total number of citations. The journal with the second highest number of manuscripts (n=14) was the Journal of Clinical Oncology with the highest number of total citations (9211) with a 2018 impact factor of 28.245. This journal also published the highest cited manuscript by Stein et al. [15]. Interestingly, high impact factor journals such as Nature, Lancet and the New England Journal of Medicine (2018 impact factors 43.07, 59.102 and 70.67 respectively) had fewer publications and total number of citations within the top 100 list. However, the manuscript with the highest citation rate (399.7) by Rosenberg et al. [32] was published in

the Lancet in 2016. High impact factor journals usually publish articles from several medical disciplines appealing to a wide-ranging audience. It is likely that a higher number of bladder cancer based manuscripts were published in urology and oncology specific journals due to the subspecialised topics addressed in the articles.

Bibliometric analysis can be useful to identify key themes and publications within a given specialty but may be limited by several types of bias. Manuscripts may be cited repeatedly because of professional bias, self-citation, institutional and language biases. An additional limitation is the inclusion of first and senior authors, and the institution of the first author. It is conceivable that many first authors also co-authored other manuscripts within the top 100 list and hence may be under-represented in the present study format [14]. Historic articles may also receive a higher number of citations because of the duration of availability to the public and do not genuinely reflect the impact of an article. Time bias can be reduced by applying a citation rate, which is calculated using the number of citations of a manuscript divided by the years since its publication. The use of a citation rate has its own limitation due to publication lead-time, resulting in significant articles requiring a period of time to garner citations. Lastly, search analyses of manuscripts in which their titles do not contain pertinent key words relating to bladder cancer may have been missed despite multiple search terms employed in the database interrogation.

## **5. Conclusion**

This study has identified the most influential articles in the field of bladder cancer that have served to further our knowledge of the disease. Furthermore, as well as identifying that pathobiology and oncological treatment are the most prominent themes within the bladder cancer literature, this bibliometric analysis provides useful information and insight for clinicians and researchers as to what forms a highly citable article in this field.

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