The Journal of Health Design

REVIEW

Factors impacting the delay in diagnosis and treatment of testicular cancer: A systematic review

Rose Clarke, Thomas Williams

University of Notre Dame, Australia

To Cite: Clarke R, Williams T. Factors impacting the delay in diagnosis and treatment of testicular cancer: A review. JHD. 2022;7(2):465–485
https://doi.org/10.21853/JHD.2022.164

Corresponding Author:
Rose Clarke
Melbourne Clinical School
University of Notre Dame
Melbourne, VIC, Australia
roseclarke17@gmail.com

SUMMARY
Early diagnosis and management of testicular cancer can improve mortality and prognosis. This systematic review found extensive patient-, physician-, and system-related factors that increased the length of time to diagnosis. Future preventative strategies should target the modifiable factors such as lack of awareness, embarrassment, accessibility, general practitioner education, and clinical training and streamlined imaging processes.

Key Words
Testicular cancer; delayed diagnosis; delayed treatment

ABSTRACT

Background

Testicular Cancer (TC) has a high cure rate when diagnosed early. However, delays in diagnosis and treatment still exist and are associated with greater disease progression and poorer prognosis.

Aims

This systematic review has two aims: 1) identify the major patient-, provider-, and system-related factors associated with diagnostic and treatment delay of testicular cancer; and 2) establish the impact that each factor has on the total length of delay.

Method

The researchers conducted a systematic review of the literature between 1996 and 2020 in the electronic databases CINAHL and MEDLINE in accordance with the PRISMA guidelines. In total, 303 articles were identified and 15 were included in the final review.

Conclusion

This systematic review identified several factors contributing to diagnostic delay at each of the three levels (patient, provider, and system) along the diagnostic pathway. Type of TC, lack of awareness, embarrassment, misdiagnosis, and referrals for ultrasound scans were associated with longer diagnostic and treatment delays. Many of these factors are modifiable, except for the subtype of TC, allowing for interventions to be implemented and reducing diagnostic delays in the future.

BACKGROUND

Testicular cancer (TC) is the most common solid tumour in men aged 20–34, accounting for 1–2 per cent of all tumours in males, with its incidence increasing in industrialised countries.[1,2] Despite effective therapies in TC treatment, patient hesitations, misdiagnoses, and system delays continue to hinder early diagnosis and prognosis for some TC patients.[3]

Research has shown that the average length of diagnostic delay for TC (mean 26 weeks) has remained relatively stable over the last 40 years.[4] Greater delays in diagnosis lead to higher stages of TC at presentation and consequently poorer long-term survival rates.[5,6] However, limited research has sought to investigate the various factors that contribute to this delay.

The prognosis and management options of TC is dependent on the histological subtype. Most literature broadly categorises TC into two main types: seminoma and non-seminomatous germ cell tumours (NSGCT). Seminoma is the most common type of TC and tends to have more favourable outcomes due to its limited metastatic potential in comparison to NSGCT. For most patients with limited stage disease of TC, the prognosis is greater than 95 per cent.[6] However, in men presenting with metastatic or aggressive disease, a cure for a disease-free state is only achievable in 50–70 per cent of patients. This discrepancy in prognosis forms the foundations for why it is important to reduce the diagnostic delay for TC patients.[6]

In the early 2000s, the United Kingdom trialled the introduction of novel "2-week wait referral" clinics for TC. Any suspected TC patients were to be reviewed by a specialist within a two-week period from seeing their general practitioner (GP) at these highly specialised TC clinics. The UK Department of Health hoped that more streamlined administration, easier access to specialists, and ultrasound imaging may reduce delays in diagnosis by improving system processes.[7]

However, the literature shows that diagnostic delay can occur anywhere along the diagnostic pathway. Diagnostic delay could be due to factors pertaining to the patient delaying presentation to the doctors, due to the provider (being either the primary care physician or specialist), or related to errors within the hospital system itself. Some factors have been reviewed in the past, including age, socioeconomic status, lack of awareness, and embarrassment.[2,8,9] This systematic review will accumulate and interpret data relating to diagnostic and treatment delay of TC patients at these various diagnostic pathway intervals.

METHOD

This systematic review was conducted in accordance with the PRISMA Guidelines (Figure 1).

One author developed a search strategy, including thesaurus terms, MeSH subject headings, and keywords. The second author reviewed the search strategy before it was applied to MEDLINE and CINHAL via EBSCO host. The full search strategy included:

[(MM "Delayed Diagnosis") OR (MM "Diagnosis, Delayed") OR (MM "Referral and Consultation") OR (MM "Primary Health Care") OR (MM "Secondary Health Care") OR (MM "Secondary Care Centers") OR (MM "Tertiary Care Centers") OR (MM "Patient Acceptance of

Health Care") OR (MM "Primary Care Centres") OR (MM "Diagnosis") OR (MM "Failure to Diagnose") OR (MM "Treatment Delay") OR (MM "Patient Attitudes") OR ("delay*") N2 ("diagnos*") OR "Clinician* delay*" OR "Clinical delay*" OR "secondary care diagnos*" OR "secondary care delay*" OR "referral delay*" OR "total delay*" OR "total patient delay*" OR "primary care delay*" OR "patient delay*" OR "provider delay*"]

AND

[(MH "testicular neoplasms") OR (MH "Neoplasms, Germ Cell and Embryonal") OR (MH "Seminoma") OR (MM "Testicular Self Examination") OR (MH "Sertoli-Leydig Cell Tumor") OR (MM "Choriocarcinoma, Non-gestational") OR (MM "Teratocarcinoma") OR (MH "Germinoma") OR "sertoli-leydig cell tumo*" OR "yolk sac carcinoma" OR ("testes" or "testicular") N2 ("cancer*" or "neoplasm*") OR ("testes" or "testicular") N2 ("germ*" or "Cell") OR ("testicular tumo*")]

The authors limited the search to literature in English, male primary testicular cancers, and published between January 1, 1996 and January 1, 2020. The two authors initially screened all articles by title and abstract independently and then they assessed relevant full-text articles for eligibility. Both authors followed the full inclusion and exclusion criteria (Figure 1); they flagged and resolved any disagreements in consultations with their research supervisors. The authors present the overall characteristics, including study design and critical appraisal of included articles (Table 1).

Due to the heterogeneity of data, including outcome measures, wait time intervals, and study designs, statistical analysis of the data was precluded and therefore the authors did not perform any meta-analysis. However, they pooled and presented all reported data as factors specific to the patient, provider, or system (Tables 2–5).

RESULTS

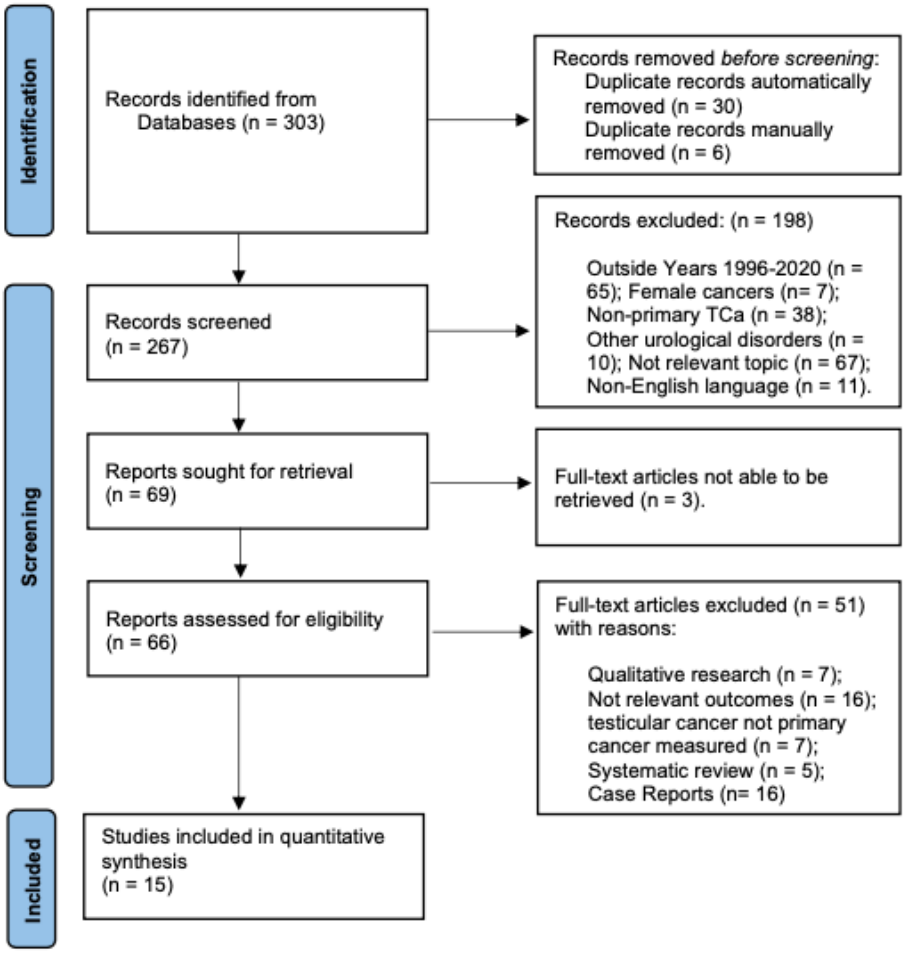
Study Selection: Database search generated 303 articles, of which 37 were duplicates (Figure 1). After screening and assessing for relevance, a total of 15 articles met the eligibility criteria and were included in this study (see Table 1 for overall study characteristics).

Characteristics of Delay by Diagnostic Time Intervals

Thirteen articles reported a time interval along the diagnostic pathway of TC, ranging from symptom onset to GP review, or specialist review to surgical intervention of TC (summarised in Table 2).[2,6–17]

Overall Diagnostic Delay: Three articles from 2004–2011 found that the overall delay, represented as the time from symptom onset to surgery, orchidectomy, was consistent with a median of 58–61 days.[2,12,15] Based on the type of TC, Huyghe et al.[2] found that NSGCT had statistically shorter overall delays (median 85 days) than seminomas (median 149 days).

Figure 1: PRISMA flow diagram of screening process and eligible articles published between January–April 2020



Patient Delay: The length of patient delay for TC cases was 14–42 days, as recorded as the median time to presentation from symptom onset (SI).[6,8,9,12,13,17] Two articles found that NSGCT presented to a doctor earlier than those with seminoma, corresponding to shorter patient delays.[7,16] Connolly et al.[12] found that 80 per cent of patients had a patient delay (SI) greater or equal to their diagnostic interval (DI).

Provider Delay: Nine articles reported a provider delay, represented as the time from first presentation to diagnosis (DI), median 5–164 days, or the time from GP to specialist review, median 1–56 days.[6,7,9,11–14,16,17] Based on the type of TC, Connolly et al.[12] found that there was no statistically significant difference in provider delay. However, one article found that the novel "2-week wait" referral system reduced the time from GP to specialist review ($p<0.05$).[7] Equally, the novel system was effective in so far as 96 per cent of "2-week wait" referrals were reviewed within the appropriate timeframe.[14]

System Delay: Five articles assessed the system delay interval, represented as the time from the doctors consult to surgical intervention, which had a median delay of 5–32 days.[6,7,10,12,17]

Kumaraswamy et al.[7] found there was no statistically significant association between the "2-week wait referrals" and the time to surgical intervention.

1. Patient Delay

Six articles reported on patient-related factors, which represented reasons why a patient delayed their presentation to a primary care physician and consequently may have contributed to delays in diagnosis of TC (Table 3).

Lack of Awareness and Attribution of Symptoms: Two articles found that a large majority of people had heard of TC prior to diagnosis, ranging from 52–91 per cent, however, this had no statistical significance on the length of diagnostic delay.[9,12] However, 54–65 per cent of patients who noticed scrotal changes did not attribute their new symptoms to TC.[9,12] In fact, Öztürk et al.[9] found 30 per cent attributed their symptoms of scrotal change to other causes.

Fear of Diagnosis and Embarrassment: Connolly et al.[12] had a subgroup of TC patients with a diagnostic delay of greater than 1 year, of which 44 per cent of cases were due to lack of awareness of TC, 32 per cent said that the fear of a diagnosis delayed them from presenting to a doctor, 8 per cent were embarrassed, and 16 per cent cited lack of access. Öztürk et al.[9] found significantly longer diagnostic delay in the 45 per cent of TC patients that reported a degree of embarrassment.

Lack of Access: Two studies reported lack of access to health services as a reason for delay.[10,12] In fact, patients had statistically significant longer treatment delays if they did not have private insurance or lived more than 50 miles from a treatment centre.[9]

Education: Two studies found that patients with higher educational levels have significantly shorter diagnostic and treatment delays.[9,10] However, Toklu et al.[16] found no association between education levels and delay in those that completed tertiary education compared to those who had completed secondary education or less.

Patient Characteristics: Marital status did not contribute to diagnostic delay.[9,16] However, four articles reported age as a factor.[8–10,16] Two articles found a statistically significant longer diagnostic delay in the subgroup aged >35 year[8] and a longer treatment delay in group aged >40 years.[10] However, no association with age was found in the other two articles.[9,16] Macleod et al.[10] also found that treatment delay was negatively associated with low-income residences and Hispanic and Black races.

2. Provider Delay

Thirteen articles reported provider-related factors that referred to reasons relating to the primary care or secondary care physician that may have contributed to delay in confirming diagnosis of TCa (Table 4).

Presenting Symptoms: Seven studies found that the most common presenting symptom, in up to 81 per cent of cases, was testicular enlargement, which was either painful or painless.[2,6,7,9,11–18] The classic painless scrotal mass usually presented in around 48 per cent of cases.[2,16,19] However,

Wilson et al.[15] reported 77 per cent painless testicular enlargement, and Toklu et al.[16] reported only 22 per cent with a self-discovered painless mass. Testicular pain was only present in up to 49 per cent of cases.[2,12,15,16,19] In those presenting to their GP, 86 per cent had testicular changes, while the remaining 14 per cent had metastatic symptoms (Table 4). Connolly et al.[12] found metastatic symptoms led to a significantly longer delay in diagnosis. Öztürk et al.[9] found no significant association in the diagnostic delay in those that presented with metastatic or testicular changes. Other less common presenting symptoms were a history of scrotal trauma, which led to a misdiagnosis and subsequently a delayed diagnosis.[12]

Misdiagnosis: Seven articles reported misdiagnosis as a provider-related factor.[6,7,9,12–14,19] In the year prior to diagnosis, two studies found around 13 per cent of TC cases were misdiagnosed,[11,18] and that TC cases consulted the GP twice as often in this period.[19] The most frequent misdiagnosis in up to 84 per cent of cases was epididymitis/orchitis.[9,12,13,19] Öztürk et al.[9] found that 54 per cent of those presenting with testicular change and 50 per cent presenting with symptoms other than testicular changes were misdiagnosed and consequently correlated to a diagnostic delay ($p<0.05$).

Inappropriate Management: As a consequence of misdiagnosis, four studies found the most commonly reported inappropriate management was antibiotics for suspected epididymitis.[9,12,13,19] Within this subgroup, both Connolly et al.[12] and Öztürk et al.[9] found this delay the diagnosis of TC cases.

Challenges of Clinical Examination: Five articles reported various clinical challenges that were associated with a delayed diagnosis.[7,11,14,15,18] In up to 33 per cent of diagnosed TC cases, these cases had normal clinical examination findings or no signs of malignancy on examination.[7,11,15,18] In fact, in 59 per cent of "non-2-week wait" referral cases, the GP and specialist disagreed on examination findings.[14] In up to 87 per cent of GP referrals for suspected TC, they were subsequently diagnosed as benign disease or even normal variants of the epididymis.[14,18] One article found that 1 per cent of referrals explicitly stated that the primary care physician had not even examined the patient before referring them for suspected TC.[7]

3. System Delay

Four studies reported system-related factors, which referred to any identifiable factor within the hospital system, including referral routes or increased need for investigations that may have contributed to delays in the diagnosis and treatment of TCa (Table 5).

Inappropriate Referral Patterns: The criteria for the "2-week wait" referral system in the UK was the detection of a testicular lump.[14] Three articles assessed the "2-week wait" referral system and up to 81 per cent were inappropriately referred by the GP to the clinic, defined as not meeting the referral criteria and rather prioritised based on the physician's level of malignancy suspicion. Foster et al.[14] found that the GP and specialists only agreed on the prioritisation category in 53 per cent of referrals. Only up to 64 per cent of TC cases were actually referred under the "2-week wait" rule.[7,14,18]

Administrative Processes: One study suggested that 33 per cent of delays to flaws in the hospital administrative processes were associated with a subgroup where longer diagnostic delays existed.[12] Alternatively, Kumaraswamy et al.[7] reported that the "2-week wait referral" system significantly shortened diagnostic delay due to the more streamlined administration processes between the initial GP referral and the clinic.

Investigative Delays: Rochester et al.[18] reported difficulties in recruiting a sonographer that led to delayed diagnostic ultrasounds (up to 22 weeks rather than 2 weeks) which consequently led to prolonged diagnosis of TCa.

DISCUSSION

In this study, overall trends in diagnostic delay are relatively constant from 1996–2020.

Seminoma cancers generally have a slower disease progression and tend to be confined to the testes when compared to NSGCT. Consistent with previous literature,[20] our study found that seminomas led to a markedly longer time to presentation compared to NSGCT[8,17] and an overall longer delay from symptom onset to treatment.[2,15] However, the type of TC had no impact on the time taken for a diagnosis.[12] The differences in delay by type of TC may be due to the indolent symptomatology of seminomas or may be due to embarrassment related to discussion of genital-related issues leading men to present to their doctor later. On the other hand, NSGCT present much earlier, but may present in non-specific ways, including metastatic symptoms that can contribute to greater rates of misdiagnosis and inappropriate treatment.

This study also found that a longer patient delay was associated with patient embarrassment and lack of awareness. Conversely, shorter patient delays were found in those with a higher educational level.[9,10,12] Lower socioeconomic status and need to travel more than 50 miles for care were both associated with delays in treatment.[10,12] The lack of access and affordability of healthcare services is not specific to TC but rather an issue reflected across the wider medical field and community.

Around 95 per cent of TC patients presented to their GP as their initial point of contact with the healthcare system.[9] Consistent with previous literature,[1] testicular enlargement or lump was the most common presenting symptom followed by testicular pain. However, patients with testicular pain alone had no significant abnormalities found on physical examination. Equally, testicular pain, especially on the background of scrotal trauma, is more commonly associated with significant pathologies other than malignancy and may contribute to a proportion of the misdiagnosis category. Ultimately, patients presenting with only testicular pain highlights some of the many challenges placed on physicians to accurately and quickly diagnose TC based on physical examination alone. It can also account for why TC patients were more likely to present to their GP twice as often as control patients in the year prior to diagnosis.[19] Consequently, up to 93 per cent of suspected TC referrals required a scrotal ultrasound to diagnosis the underlying malignancy.[7,11,15]

The impact of the delays at the system level were limited by the small representation of articles. However, of the studies that examined the novel "2-week wait referral" system proved to have had some benefits in reducing the diagnostic interval by shortening the time from primary care referral to specialist clinic. However, it failed to impact on the time from consult to treatment. These studies found that primary care physicians exploited the TC clinics with high numbers of inappropriate referrals that broke referral protocol and even referred some patients without being examined first.[7,14,18] Therefore, considering the cost and limited impact on improving overall delays in diagnosis but not treatment of TC, re-implementation of the "2-week referral" clinics should not be a high priority for future strategies.

Limitations

All efforts were made through the systematic review to accomplish reproducibility and statistical significance. Despite these efforts, some limitations should be noted. Due to the heterogeneity of the data with time intervals and the definition of delay not being standardised across the literature, no metanalysis could be performed. A low prevalence of TC in the general population led to variable sample sizes and a small pool of articles to choose from, reducing the power of the study. Similarly, some articles used in the review relied on retrospective data and questionnaires, so we are unable to exclude the possibility of recall bias and miscalculations of dates, including date of symptom onset.

Clinical and Future Implications

Previous studies have found that public health awareness campaigns are more effective than testicular self-examinations in improving the time from first noticing symptoms to presenting to a health professional.[2] In fact, the US Preventive Services Task Forces recommends against screening for asymptomatic testicular cancer.[20]

Therefore, the three major future approaches should be as follows: 1) increasing awareness about TC at the patient level, such as within schools, to normalise the condition and reduce stigma associated with talking about testicular changes; 2) the need for ongoing clinical development with GPs to recognise the symptomatology of TC for patients that present in the appropriate age group; and 3) consideration of an improved streamlined referral protocol that mandates the use of ultrasound earlier in the diagnostic pathway of TC, which will improve delays associated with both the provider and the system.

CONCLUSION

Although system factors can contribute to the length of delay of TC, this review found a significant number of factors can still be attributed to the patient and the physician. Many patient factors were associated with diagnostic delay, including education levels, lack of awareness, and perceived embarrassment. Provider delay factors included misdiagnosis and inappropriate management. Conversely, diagnostic delay was reduced at the system level in studies trialling a novel "2-week-wait" referral system for suspected TC.

Considering the type of TC is non-modifiable, future strategies, including increased public awareness of TC in schools, GP clinical development, and improved streamlined referrals to

ultrasound scans, should be implemented to address the modifiable factors to reduce diagnostic delay. Ultimately, a reduction in diagnostic or treatment delay will lead to patients presenting with an earlier stage of TC and therefore improved prognosis and survival rates.

REFERENCES

1. Bosl GJ, Vogelzang NJ, Goldman A, et al. Impact of delay in diagnosis on clinical stage of testicular cancer. Lancet (London, England). 1981;2(8253):970-3.
2. Huyghe E, Muller A, Mieusset R,et al. Impact of diagnostic delay in testis cancer: results of a large population-based study. European urology. 2007;52(6):1710-6.
3. Post GJ, Belis JA. Delayed presentation of testicular tumors. Southern medical journal. 1980;73(1):33-5.
4. Moul, JW. Timely diagnosis of testicular cancer. The Urologic clinics of North America. 2007; 34(2):109.
5. Thornhill JA, Fennelly JJ, Kelly DG, et al. Patients' delay in the presentation of testis cancer in Ireland. British journal of urology. 1987;59(5):447-51.
6. Vasudev NS, Joffe JK, Cooke C, et al. Delay in the diagnosis of testicular tumours – changes over the past 18 years. British Journal of General Practice. 2004;54(505):595-7.
7. Kumaraswamy P, Cox R, O'Rourke JS, et al. Audit of two-week rule referrals for suspected testicular cancer in Cornwall, 2003-2005. Annals of the Royal College of Surgeons of England. 2009;91(3):239-44.
8. Kobayashi K, Saito T, Kitamura Y, et al. Effect of the time from the presentation of symptoms to medical consultation on primary tumor size and survival in patients with testicular cancer: Shift in the last 2 decades. Urologic Oncology. 2014;32(1):43.e17-22.
9. Öztürk Ç, Fleer J, Hoekstra HJ, et al. Delay in Diagnosis of Testicular Cancer; A Need for Awareness Programs. PloS one. 2015;10(11):e0141244.
10. Macleod LC, Cannon SS, Ko O, et al. Disparities in Access and Regionalization of Care in Testicular Cancer. Clinical genitourinary cancer. 2018;16(4):e785-e93.
11. Carey K, Davis NF, Elamin S, et al. A novel rapid access testicular cancer clinic: prospective evaluation after one year. Irish journal of medical science. 2016;185(1):215-8.
12. Connolly SS, Daly PJA, Floyd MSJ, et al. Terminology and details of the diagnostic process for testis cancer. The Journal of urology. 2011;185(3):876-80.
13. Ondrusova M, Ondrus D. Epidemiology and treatment delay in testicular cancer patients: a retrospective study. International urology and nephrology. 2008;40(1):143-8.
14. Foster PW, Ritchie AWS, Jones DJ. Prospective analysis of scrotal pathology referrals - are referrals appropriate and accurate? Annals of the Royal College of Surgeons of England. 2006;88(4):363-6.
15. Wilson JP, Cooksey G. Testicular pain as the initial presentation of testicular neoplasms. Annals of the Royal College of Surgeons of England. 2004;86(4):284-8.
16. Toklu C, Ozen H, Sahin A, et al. Factors involved in diagnostic delay of testicular cancer. International urology and nephrology. 1999;31(3):383-8.
17. Hernes EH, Harstad K, Fosså. Changing incidence and delay of testicular cancer in southern Norway (1981-1992). European urology. 1996;30(3):349-57.
18. Rochester M, Scurrell S, Parry JRW. Prospective evaluation of a novel one-stop testicular clinic. Annals of the Royal College of Surgeons of England. 2008;90(7):565-70.
19. Shephard EA, Hamilton WT. Selection of men for investigation of possible testicular cancer in primary care: a large case-control study using electronic patient records. British Journal of General Practice. 2018;68(673):e559-e65.
20. Moul JW, Paulson DF, Dodge RK, et al. Delay in diagnosis and survival in testicular cancer: impact of effective therapy and changes during 18 years. The Journal of urology. 1990;143(3):520-3.

21. U.S. Preventive Services Task Force: Screening for testicular cancer: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 154 (7): 483-6, 2011.

ACKNOWLEDGEMENTS

Many thanks to Dr Catherine Krejany and Professor Moyez Jiwa for their ongoing support.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

ETHICS COMMITTEE APPROVAL

None

Table 1: Overview of studies included in the systematic review

Author & Year	Title	Study Design	Sample Size	Country	Delay Measured	Critical Appraisal
Shephard et al.[19] (2018)	"Selection of men for investigation of possible testicular cancer in primary care: a large case-control study using electronic patient records"	Retrospective Case-Control	n=1398	United Kingdom	Provider Delay	–Large data loss –40% outcomes statistically significant –Recall bias potential
Macleod et al.[10] (2018)	"Disparities in Access and Regionalization of Care in Testicular Cancer"	Retrospective Cohort	n=31,522	America	Patient Delay	–Coding and retrospective bias –39% of data not included –Cofounding factors not recorded –Causation and correlation not distinguishable
Carey et al.[11] (2016)	"A novel rapid access testicular cancer clinic: prospective evaluation after one year"	Prospective Cohort	n=74	Ireland	Provider Delay	–No statistical analysis completed –Cofounding factors not recorded
Öztürk et al.[9] (2015)	"Delay in Diagnosis of Testicular Cancer; A Need for Awareness Programs"	Cross Sectional	n=66	Netherlands	Patient Delay Provider Delay	–Strong response rate (91%) –Small sample size –Potential for recall bias
Kobayashi et al.[8] (2014)	"Effect of the time from the presentation of symptoms to medical consultation on primary tumour size and survival in patients with testicular cancer: Shift in 2 decades"	Retrospective Cohort	n=175	Japan	Patient Delay	–Results not statistically significant –Small patient size –Potential for recall bias
Connolly et al.[12] (2011)	"Terminology and details of the diagnostic process for testis cancer"	Retrospective Cohort	n=100	Ireland	Patient Delay Provider Delay System Delay	–Definition of outcomes consistent –No statistical analysis –Small sample size
Kumaraswamy et al.[7] (2009)	"Audit of two-week rule referrals for suspected testicular cancer in Cornwall, 2003-2005"	Retrospective Audit	n=241	United Kingdom	Provider Delay System Delay	–Cofounding factors not recorded –Correct statistical analysis completed
Rochester et al.[18] (2008)	"Prospective evaluation of a novel one-stop testicular clinic"	Prospective Audit	n=1017	United Kingdom	Patient Delay System Delay	–Results statistically significant –Cofounding factors not recorded –Misdiagnosis not accounted for
Ondrusova et al.[13] (2008)	"Epidemiology and treatment delay in testicular cancer patients: a retrospective study"	Retrospective Cohort	n=1,832	Slovakia	Provider Delay	–No statistical analysis done –Potential for recall bias –Low response rate 73%

Huyghe et al.[2] (2007)	"Impact of diagnostic delay in testis cancer: results of a large population-based study"	Prospective Cohort	n=439	France	Provider Delay	–Cofounding variables not accounted for –Potential for recall bias –Results statistically significant –Definitions of outcomes consistent
Foster et al.[14] (2006)	"Prospective analysis of scrotal pathology referrals - are referrals appropriate and accurate?"	Prospective Cohort	n=201	United Kingdom	Provider Delay System Delay	–Statistically significant results –Cofounding factors not recorded –Exposures and outcomes measured appropriately
Wilson et al.[15] (2004)	"Testicular pain as the initial presentation of testicular neoplasms"	Retrospective Cohort	n=118	United Kingdom	Provider Delay	–Small sample size –Outcome not specifically defined –Potential for recall bias –Patient pool reduced with incorrect search terms
Vasudev et al.[6] (2004)	"Delay in the diagnosis of testicular tumours–changes over the past 18 years"	Prospective Cohort	n=180	United Kingdom	Patient Delay Provider Delay	–Small return rate (50%) –Outcomes not specifically defined –No statistical analysis completed
Toklu et al.[16] (1999)	"Factors involved in diagnostic delay of testicular cancer"	Retrospective Cohort	n=140	Turkey	Patient Delay Provider Delay	–Small sample size –Results not statistically significant –Cofounding factors not recorded
Hernes et al.[17] (1996)	"Changing incidence and delay of testicular cancer in southern Norway (1981–1992)"	Retrospective Cohort	n=352	Norway	Provider Delay	–Small delay population 61% –Delay not statistically significant –Cofounding factors not recorded

Table 2: Characteristics of delay in the pathway of testicular cancer diagnosis

	Patient Delay	**Provider Delay**		**System Delay**	**Overall Delay**
	Time from Symptom Onset to First Consult (SI) Median days (range)	**Time from GP to Specialist Review** Median days (range)	**Time from First Presentation to Diagnosis (DI)** Median days (range)	**Time from GP or Specialist Consult to Surgical Intervention** Median days (range)	**Time from Symptom Onset to Surgical Intervention** Median days (range)
Macleod et al.[10] (n=31,522)				10.2% had a delay of > 11 days to orchidectomy, which was >90th percentile of all time to orchidectomy	

Carey et al.[11] (n=74)		Delay in all cases: Mean 6 (0–26) Benign Dx: 5 (0–26) Malignant Dx:1 (0–11)		Delay in all cases: Mean 6 (1-61). Benign Dx: 32 (3-61). Malignant Dx: 3 (1-5)	
Öztürk et al.[9] (n=66)	Mean SI: 30 (1–365) 95% visited GP: 14 (0–252) 5% visited ER or Urologist: 14 (1–180)	In the 95% that presented to GP: 7 (0–240) Of the subgroup who consulted their GP with a scrotal change at their first visit (n=49); 41% had specialist review within 3 days (0–3), 31% between 5-14, 28% within 51 (17–240).			
Kobayashi et al.[8] (n=175)	68% presented in <6months: Of this; 65.5% seminoma, 34.5% NSGCT 42% presented >6 months: Of this; 82.1% seminoma,17.9% NSGCT [a]SI in 1991-2000 patients: 74 days (p=0.042). 70.2% presented in <6 months [b]SI in 2000-2010 patients: 104days. 64.8% presented in <6months				
Connolly et al.[12] (n=100)	SI: 29 (0–720) In 80% of cases SI exceeded or was equal to DI		Overall DI: 7 (1–540). 68% in <7days, 19% in 7 to 30 days, 13% in >30 days. [X]Seminoma group: DI= 86 days [X]NSGCT group: DI=85 days.		Mean 88 days (SD+/- 122)
Kumaraswamy et al.[7] (n=241)		Pre 2-week wait rules: 16 (SD +/-13.2) [a]Post 2-week wait rules: 6.8 (SD+/-5.1)		Pre 2-week wait rules: [X]Referral to Operation: 41.8 (SD+/-35.3) [X]Clinic to Operation: 25.7 (SD+/-31.3)	

				Post 2 week rule: [X]Referral to Operation: 31.8 (SD+/-27.3) [X]Clinic to Operation: 25 (SD+/-25.5)	
Ondrusova et al.[13] (n=1,807)	Data only analysed for 7.9% of cases: Median: 35 (0–3,267)	Data only analysed in 5.9% of cases: Mean of 5.7, Median 1 (0–90)	Data only analysed in 19% of cases: Median 5 (0–2,980), Mean 20.1		
Huyghe et al.[2] (n=439)					Median 61 (30–1095) [b]44.6% Seminoma: 149 days (SD+/-186) [a]55.3% NSGCT: 85 days (SD+/-122) In subgroup DD <3mo (72%): 63% had Seminoma, 79% NSGCT In subgroup DD= 4–6mo (14%): 16% Seminoma, 13% NSGCT In subgroup DD >6mo (14%): 21% Seminoma, 7% NSGCT
Foster et al.[14] (n=201)		Median 56 days In the subgroup of 2-week referral patients (n= 53), 96% were seen within required 2 wks.			
Wilson et al.[15] (n=118)					Overall: 6 (SD± 138). 52% Seminoma: 58 (1–728) 20% NSGCT: 6.1 (7–153)
Vasudev et al.[6] (n=180)	Median 14 days 16% presented >61 days, 4% presented >83 days	Median 15 days 48% seen within < 14 days, 86% seen <61 days, 4% seen >61 days		Median 5 days 8.4% had >28 day delay	
Toklu et al.[16] (n=140)			[X]Median 164 days. 46% had DI <30 days, 44% had DI 30-365 days, 10% DI >365 days		

Hernes et al.[17] (n=352)	[X]Overall: median 42 days 42% cases >91 days NSGCT: 27 days Seminoma: 61 days		Median 14 (0–272)	Median 32 (1–84)	

Abbreviations: Dx=diagnosis, DD=diagnostic delay DI=diagnostic interval, SI=symptom interval
[a]Positive association on TC diagnostic or treatment delay (p<0.05)
[b]Negative association on TC diagnostic or treatment delay (p<0.05)
[X]No association to TC diagnostic or treatment delay (p>0.05)

Table 3: Factors related to patient delays in the diagnosis of testicular cancer

	Lack of awareness	Attribution of Symptoms	Fear of Diagnosis	Embarrassment	Lack of Access	Education	Patient Characteristics (SES, Age, Marital Status, Race)
Macleod et al.[10] (n=2935					In the orchiectomy delay subgroup: Insurance: 9.6% privately insured, [b]13.2% Medicaid, [b]15.6% Medicare, [b]11.3% uninsured, 9.6% data missing. Travel Distance: 9.7% <50miles, [b]15% >50miles	In the orchiectomy delay subgroup; 11.8% (<79% population completed HS), 11.2% (79%-87% completed HS), [a]10.1% (87.1-93% completed HS), [a]9.3% (>93% completed HS), 12% data missing	In the orchiectomy delay subgroup: Median Income of Residence: 11.2% (<$38K), 10.3% ($38–47.9K), 10.5% ($48–62.9K), [a]10% (>$63K), 10% data missing Race: White 10%, [b]Hispanic 11.4%, [b]Black 11.9%, Asian 11%, other 9.8% Age: 16.5% <25yrs, 51.7% <25-39, [b]31.8% >40yr
Öztürk et al.[9] (n= 60)	[X]52% had heard of TC before diagnosis. [X]48% of patients experiencing testicular change (n=54) knew of TC before	[X]88% noticed a testicle change, of these (n=54): 54% did not consider a specific disease for the change, [X]30% attributed to causes, 6% inguinal hernia, 9% epididymitis, 2% sports injury, 4% Crohn's		[b]7% felt very embarrassed, 13% Quite a bit embarrassed, 42% Somewhat embarrassed, 38% Not at all embarrassed, 17% did not answer		[b]3.4% completed primary school only, 8.5% low vocational degree, 18.6% middle secondary degree, 33.9% middle vocational degree, 16.9% high secondary degree, 15.3% high vocational degree, and 3.4% completed university.	[X]Age: median 26yrs (range 17–45) [X]Marital Status: 49% had a partner, 52% did not have a partner

	diagnosis but 65% did not associate a change with cancer.	Disease, 2% gastritis, 2% hydrocele, 4% puberty, 2% dental problem, 17% no answer					
Kobayashi et al.[8] (n=175)							[a]Age Dx <6 months: 68% cases median age 35 (2-66) Dx >6months: 32% cases median age 36.5 (25–65)
Connolly et al.[12] (n=100)	In subgroup where delay >1yr: 44% Lack of Awareness, 69% Prior knowledge of disease, 18% Prior experience of TC		In the subgroup where Dx delay >1 year (n=25): Fear of diagnosis 32%	In the subgroup where Dx delay >1 year (n=25): 8% due to Embarrassment	In the subgroup where Dx delay >1 year (n=25): 16% due to Lack of Access		
Vasudev et al.[6] (n= 180)	[x]91% heard of TC prior to diagnosis Source of info: 55% via newspaper, 53% TV, 20% health leaflets, 18% radio, 15% work						

Toklu et al.[16] (n= 140)						[X]Education: Illiterate/ primary/ secondary school: TC Dx within <1mo (38%), between 1-12mo (48%), >12mo (14%) College/ Uni education: TC Dx within <1mo (50%), between 1-12mo (42%), >12mo (8%)	[X]Annual Income: < $1000/yr: Dx within <1mo (45%), between 1–12mo (43%), >12mo (11%) $1000-2000/yr: Dx within <1mo (33%), between 1–12mo (52%), >12mo (15%) > $2000/yr: Dx within <1mo (56%), between 1–12mo (40%), >12mo (4%) [X]Age: median 32yrs (range 18–51). [X]Marital Status: 80% married, 20% single

Abbreviations: TC=testicular cancer, Dx=diagnosis, HS=high school

[a]Positive association on TC diagnostic or treatment delay ($p<0.05$)

[b]Negative association on TC diagnostic or treatment delay ($p<0.05$)

[X]No association to TC diagnostic delay ($p>0.05$)

Table 4: Factors related to provider delays in the diagnosis of testicular cancer

	Presenting Symptoms	Misdiagnosis	Inappropriate Management	Challenges of Clinical Examination
Shephard et al.[19] (n=1398)	25% testicular swelling, 20% testicular lump, 13% testicular pain, 5% abdominal pain, 4% scrotal swelling, 3% groin pain	13% total misdiagnoses, of these: 84% Epididymis /Orchitis, 14% Hydrocele *TC cases consulted twice as often as controls in the year before Dx (8 to 4, respectively)		
Carey et al.[11] (n=74)				7% diagnosed with benign disease based on clinical exam findings. 93% required Dx ultrasound. In the TC cases (n=18); 33% had normal findings on clinical exam and scrotal ultrasound.
Öztürk et al.[9] (n=60)	[X]86% testicular change 5% initially reported other symptoms; 3% back pain, 2% abdominal pain [X]9% without testicular change; 2% stress, 3% pulmonary symptom, 2% stomach ache, 2% fatigue	[b]In those with testicular change (n=54), 54% were misdiagnosed – 31% epididymitis, 20% no Dx, 17% hydrocele, 10% back pain, 7% trauma, 3% inguinal hernia, 3% hernia, 3% UTI, 3% gynecomastia, 3% appendicitis [b]In those without testicular change (n=6), 50% were misdiagnosed– hyperventilation, asthma, gastritis	1 case presented straight to specialist and was misdiagnosed and treated for epididymitis and diagnosed with TC at day 42.	
Connolly et al.[12] (n=100)	86% localised symptoms. Of these; 94% reported Lump/swelling, 56% testis pain, 5% pain without swelling, 8% scrotal trauma, 1% asymptomatic on routine exam [b]14% metastatic symptoms: 21% had DI delay >30days	13% total misdiagnosis in the preceding year of diagnosis, of these: 62% epididymitis, 23% torsion, 8% epididymal cyst, [b]8% scrotal trauma	In the subgroup where diagnostic interval >30 days (n=12); 17% received antibiotics for suspected epididymitis.	
Kumara-swamy et al.[7] (n=241)		7% GP referrals misdiagnosed swelling due to previous vasectomy, of these; 18% subsequently diagnosed with TCa.		1% referrals explicitly stated GP had not examined the patient. 66% of "2-week-wait referrals" required diagnostic ultrasound. Based on initial exam, urologists Dx TC in 12% of total cases, of which only 8%

				subsequently confirmed. Dx benign epididymal swellings on exam in 9% of the confirmed TC (n=23).
Ondrusova et al.[13] (n=148)		In the subgroup of misdiagnosis, the most frequent misdiagnosis in 31% of cases was orchiditis/epididymitis.	31% antibiotics, 10.1% scrotal orchiectomy, 10% puncture of testis, 8% symptomatic analgesia, 6% enucleation of a tumour in unilateral disease.	
Huyghe et al.[2] (n=439)	Overall: 48% painless testis swelling, 21% change in testicular consistency, 22% painful teste, [a]6% metastasis, 2% gynecomastia, [a]1% infertility Seminoma subgroup; 55% painless swelling, 19% change in consistency, 16% pain, 6% metastasis, 3% other NSGCT subgroup; 43% painless swelling, 23% change in consistency, 27% pain, 6% metastasis, 2% other			
Foster et al.[14] (n=201)		0.5% initially referred as benign was subsequently diagnosed as TC.		Non-2-week wait referral subgroup (n=148); 59% cases GP and specialist disagreed on examination findings. 35% of total referrals were for suspected TC; 87% subsequently confirmed benign. Of these, 62% found to be normal variants of epididymis.
Wilson et al.[15] (n=115)	77% painless testicular enlargement, 23.5% testicular pain +/- enlargement, 10% testicular pain only			10% presented with testicular pain alone and had no clinical examination findings, diagnosed on subsequent US.
Vasudev et al.[6] (n=171)		In the subgroup that GP reassured/no follow up; hydrocele, strain, normal variant in testicular size	95% presented to GP at first presentation; 40% hospital referral (+/- antibiotics/US), 29% ultrasound, 14% antibiotics, 8% antibiotics + US, 6% reassure/no follow up, 2% later review, 1% analgesia	

Rochester et al.[18] (n=1017)				In the subgroup of diagnosed testicular tumours (n=11); 91% referred for suspicion of TC. 9% referred under 'routine' referral for epididymal disease and had no clinical exam signs of malignancy.
Toklu et al.[16] (n=140)	49.3% scrotal pain, 22.1% painless scrotal mass, 40% other			
Hernes et al.[17] (n=352)	11% back pain, 7% gynecomastia, 2% others (dyspnoea, haemoptysis, cerebral symptoms)			

Abbreviations = TC=testicular cancer, Dx=diagnosis, DI=diagnostic interval, US=ultrasound
[*] Statistically significant difference ($p<0.05$)
[a]Positive association on TCa diagnostic or treatment delay ($p<0.05$)
[b]Negative association on TCa diagnostic or treatment delay ($p<0.05$)
[X]No association on TCa diagnostic delay ($p>0.05$)

Table 5: Factors related to system delays in the diagnosis of testicular cancer

	Inappropriate Referral Patterns	Administrative Processes	Investigative Delays
Connolly et al.[12] (n=100)		In the subgroup where DI >30 days (n=12); 33% due to unclear cause and represents flaw in administrative process.	
Kumaraswamy et al.[7] (n=241)	Under the "2-week wait" referral system, 48% of referrals did not fit the referral guidelines. 18% of these flagrantly broke referral protocol. Only 8% were diagnosed TC cases; 0% of these were made from the inappropriate referrals.	[b]More streamlined administrative process in post "2—week-wait" referral system leads to average 9-day reduction in time from referral to clinic.	
Rochester et al.[18] (n=1017)	In the subgroup that had a radical orchiectomy (n=11); 91% TC cases, 9% benign. 45% of these referred under "2-week wait" referral, 36% urgent letter, 9% urgent ultrasound, 9% routine referral. 20% of cases were referred for scrotal lump; 4% of scrotal lump referrals were under the "2-week wait" rule for suspected malignancy.		[b]General Ultrasound–wait time range (2–22wks) due to delay in recruitment of sonographer. [b]Intravenous Urography- wait time range (7–22wks). CT scan- wait time range (5–11wks).

Foster et al.[14] (n=201)	*GP and specialists agreed on the prioritisation category of 53% cases. In the "2-week wait" referral subgroup (n=53); 81% were inappropriately referred. It was thought that the recategorization of priority should have been: 18% "2-week wait", 11% "urgent", 30% "soon", 40% routine. Only 64% of the TC cases (n=14) were referred under the '2-week wait' rule.		

Abbreviations: TC=testicular cancer, DI=diagnostic interval
*Statistically significant difference (p<0.05)
[a]Positive association on TC diagnostic or treatment delay (p<0.05)
[b]Negative association on TC diagnostic or treatment delay (p<0.05)