Review Article

Novel approaches to redesign surveillance strategies following orchiectomy for localized testicular cancer: a narrative review

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Background and Objective: Surveillance is the preferred management strategy for most men with clinical stage I testicular cancer after orchiectomy. However, frequent office visits, imaging tests, and laboratory studies place a significant burden on patients, which may contribute to poor compliance with guideline-recommended surveillance regimens. Identifying strategies to overcome these barriers may help improve quality of life, reduce costs, and improve adherence for patients. We reviewed evidence for three strategies that may help with surveillance redesign: telemedicine, implementing microRNA (miRNA) as a biomarker, and novel imaging protocols.

Methods: A web-based literature search for novel imaging strategies, diagnostic utility of miRNA, and telehealth as they relate to early-stage testicular germ cell cancer was completed during the month of August 2022. We focused our search on contemporary PubMed-indexed and Google Scholar-registered manuscripts written in English. Supportive data sourced from current guideline statements were also included. Evidence was compiled for narrative review.

Key Content and Findings: Telemedicine is a safe and acceptable platform for urologic cancer follow-up care, but it requires further study specifically among men with testicular cancer. Access to care may either be improved or reduced depending on system- and patient-level characteristics and should be implemented with this in mind. miRNA may potentially be a helpful biomarker for men with localized disease, but further research on diagnostic accuracy and marker kinetics are needed before implementing it into routine surveillance strategies or using it to deviate from long-standing surveillance regiments. Novel imaging strategies with less frequent imaging and the use of magnetic resonance imaging (MRI) instead of computed tomography (CT) appear to be non-inferior in clinical trials. However, use of MRI requires expert radiologist availability and may be more costly with a lower ability to detect small, early recurrences when used in routine practice.

Conclusions: Using telemedicine, integrating miRNA as a tumor marker, and adopting less intensive imaging strategies may improve guideline-concordant surveillance for men with localized testicular cancer. Future studies are needed to assess the risks and benefits of using these novel approaches separately or together.

Keywords: Active surveillance; germ cell tumors; orchiectomy; testicular cancer; telehealth

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Introduction

Most patients with testicular cancer have clinical stage I (CSI) disease at initial presentation ($T_{any}N0M0S0$). In other words, malignancy is found only in the orchiectomy specimen and there is no clinical evidence of metastatic spread after evaluation with axial imaging and post-orchiectomy serum tumor markers (STMs). Although patients may undergo adjuvant treatment with chemotherapy, radiotherapy, or surgery in certain clinical situations, surveillance is the preferred post-orchiectomy management strategy for the majority of men with CSI germ cell tumors (GCTs), particularly those with pure seminoma or CSIA non-seminomatous germ cell tumors (NSGCTs) (1,2).

Surveillance is preferred because it avoids overtreatment with "unnecessary" adjuvant therapies in patients who are not destined to relapse, thereby reserving treatment and its side effects for only those who absolutely require it. Current surveillance strategies call for serial imaging with ionizing radiation, frequent blood draws for STM assessment, and a significant number of clinic visits. Patients need to take time off from work and family, travel for in-person encounters, and bear the cost of healthcare utilization, all of which is disruptive to their quality of life or exposes them to financial toxicities (3). Most importantly, these barriers may contribute to many men not having guideline-concordant surveillance or being lost to follow-up while on surveillance (4,5).

Recent developments including more widespread availability and uptake of telehealth in its various forms (video visits, telephone visits, asynchronous communications), the development of microRNAs (miRNAs) as a novel STM, and the study of alternative imaging strategies provide an opportunity to change the way surveillance is performed for men with testicular cancer. These tools, used individually or implemented together, may improve adherence to guidelines by overcoming barriers to surveillance. However, the balancing measures of appropriate and timely detection with a "non-traditional" approach also requires investigation to maintain the excellent outcomes seen in patients managed with surveillance. In this narrative review, we highlight three recent developments that we believe can address aspects of the current surveillance paradigm that are less than optimal for patients, and we discuss how these approaches may be used to redesign and improve the surveillance of men with early-stage testicular cancer in the years ahead. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-855/rc).

Methods

A web-based literature search for each of the three topics of interest (novel imaging strategies, diagnostic utility of miRNA, and telehealth) as they relate to early-stage testicular GCT was initially completed during the month of August 2022 and updated in March 2023. We focused our search on contemporary PubMed indexed and Google Scholar registered manuscripts written in English. In addition to this search, we performed a manual screening of all references from pertinent manuscripts and the most current version of available guideline statements to supplement the search. Supportive data sourced from current guideline statements included those from the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU). Three authors (RSM, CDF, AB) were involved in selecting the included manuscripts based on relevance to the topic. The narrative review checklist and search terms used are shown in *Table 1*.

Comment and evidence synthesis

Telehealth

Prior to the COVID-19 pandemic, telehealth was used sparingly in urology. A review of practices published in 2019 showed that video visits were offered along the entire continuum of clinical care (new visits, follow-ups, counseling, etc.) but were only a small proportion of a clinician's total volume (6). At that time, described barriers to care via telehealth included patient-, physician-, and system-level barriers related to lack of familiarity with telemedicine, regulatory and reimbursement concerns, as well as the absence of a reliable, secure integrated video platform at many healthcare centers. One of the few silver linings of the COVID-19 worldwide pandemic was the rapid and compulsory adoption of telehealth visits to support clinical care while avoiding direct personal contact (7). Urologists were able to quickly integrate telehealth visits into their practice and were some of the earliest adopters among all specialists (7,8). Accordingly, there was a massive increase in the proportion of visits conducted remotely compared to in person. While that proportion appears to

Table 1 The search strategy summary

Items	Specification
Date of search	August 2022, repeated March 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	["Localized testicular cancer" or "germ cell tumor" or "clinical stage I"] AND "micro RNA" OR "miRNA", "telemedicine" OR "telehealth" OR "virtual medicine", "imaging" OR "surveillance" OR "MRI" or "CT"
Timeframe	None specified
Inclusion and exclusion criteria	English language only, no study type exclusions
Selection process	RSM, CDF, AB consensus
Any additional considerations, if applicable	We also performed a manual screening of all references from pertinent manuscripts and the most current version of available guideline statements to supplement the search. Supportive data sourced from current guideline statements included those from the American Urological Association (AUA), the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU)

be returning towards pre-pandemic levels, patients and clinicians alike have appreciated the benefits of telehealth visits in certain clinical situations.

A recent systematic review on the use of telehealth in urology did not find a significant number of patients with GCT among studies in the current literature (8). Despite this, the rationale for using telemedicine for patients with GCTs on surveillance is sound since surveillance protocols often require frequent visits (some as often as every 6–8 weeks). Reducing the travel and time burden of these frequent follow-ups has clear benefits, including improved adherence to surveillance protocols, which are notoriously low for men with testicular GCT (5). In addition, most studies have shown high levels of satisfaction with video visits among patients and clinicians, at times even more so than in person (8-11). There may also be cost savings at the system and patient levels because of the aforementioned reduction in travel, overhead, and resource utilization (12).

A prior study showed that the limitation of not being able to perform physical exams during telehealth visits did not change management plans for many other urologic conditions (13). However, a physical exam remains a critical component of testicular cancer diagnosis and surveillance. Transitioning follow-up visits exclusively to telehealth will require patients to reliably perform self-examinations at home and could increase the use of ultrasonography if patients have concerns about normal physical exam findings but are unable to receive an examination from a physician. Although the United States Preventive Services Task Force (USPSTF) has given a Grade D recommendation for screening testicular self-examinations, previous studies have indicated that patients have relatively strong discriminative abilities to detect scrotal pathologies on self-exam (14,15). Men with a history of testicular cancer may be even better at detecting an abnormal physical exam finding due to prior experiences. Fortunately, the risk of a metachronous second primary GCT is only about 1–2% over a survivor's lifetime, so this should not be a frequent occurrence. Further, any self-exam concerns can be promptly evaluated with an ultrasound.

Despite the potential benefits, a more widespread adoption of telehealth raises concerns about access to care and worsening of disparities since patients who are more accepting of video visits appear to be younger, of higher health literacy, and greater socioeconomic status (6). However, patients with testis cancer tend to be young and are likely to have extensive experience with mobile platforms, thus making this a feasible path forward. Telehealth may also improve access for certain rural populations where experienced specialists would not otherwise be available due to location (10). Telehealth "second opinion" consultations or even regional virtual tumor board conferences are potential avenues to centralize expert care for a rare diagnosis and deserve exploration.

There is an ongoing study by investigators in Canada who are examining how an asynchronous, decentralized approach to surveillance rooted in mobile health can help address barriers to telehealth and facilitate better adherence to surveillance recommendations. The WATChmAN study (NCT03360994) is a randomized clinical trial for patients with CSI GCT on active surveillance in which patients are

randomized to virtual care or standard in-person care (11). The investigators primarily aim to understand safety, defined as loss-to-follow-up and compliance with active surveillance schedules, as well as incidence of relapse, delays in detection of relapse, and burden of disease at relapse. Secondary endpoints include patient satisfaction, physician acceptance, and cost. At the 2020 ASCO Annual Meeting, the investigators reported that 102 of a planned 144 patients were enrolled and split equally between each arm. They found better patient compliance in the virtual arm (89% *vs.* 73%) with shorter median compliance delays (12 *vs.* 14 days). Relapses were equal between arms and median time to relapse was marginally shorter for the virtual arm (8 *vs.* 9.5 months). Although limited by incomplete response rates and immature data, there is evidence that satisfaction is higher in the virtual arm compared to the standard arm. These results suggest that virtual care in CSI testicular cancer is feasible, acceptable, and likely safe.

Novel imaging approaches

Surveillance strategies for men following orchiectomy aim to detect recurrence or secondary cancers at a stage when further curative procedures are possible, while minimizing the burden of follow-up, as well as the potential for overtreatment and concomitant treatment toxicity. Traditional, fixed follow-up schedules may be burdensome for patients as they include visits to a specialist for examinations with cross-sectional imaging that are expensive and expose patients to contrast and radiation (16). Since relapse predictably occurs in the retroperitoneum in 90% of patients and the vast majority of relapses are not detected with STMs alone, the focus of surveillance has appropriately been imaging the retroperitoneum. As such, recurrence patterns seen in prospective and retrospective series have been used to generate stage and site-specific follow-up protocols that include computed tomography (CT) scans, chest x-rays, and STM measurements at least more than 5 years after definitive treatment. A recent review compared the guideline follow-up protocols of the ESMO, EAU, the NCCN, and the AUA, as well as selected institutional follow-up protocols like the Swedish and Norwegian Testicular Cancer Group (SWENOTECA) to highlight the discordant recommendations regarding number, time-points, and type of follow-up investigations (17). These varied recommendations exist largely due to the paucity of data demonstrating a clear best approach.

Recently, a report from The Princess Margaret Cancer Center in Toronto over four decades demonstrated that relaxing the intensity of surveillance imaging results in a significant reduction in imaging frequency and is safe (18). The potential to reduce the number of scans without compromising the oncological outcome in patients with CSI NSGCT was originally studied in a 2007 randomized trial by Rustin *et al.* In this trial, men were randomized to either CT scans of the abdomen and the chest at 3 and 12 months versus 3, 6, 9, 12 and 24 months with all other care being equal (19). Their primary outcome was relapse with either International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate- or poor-risk disease. They found no significant difference between the IGCCCG prognostic group designation at the time of recurrence, but these were rare events (0.8% *vs.* 0.6%). Interestingly, the first indication of relapse was via STM only in roughly 40% of patients in both arms.

Similarly, findings recently published from the Trial of Imaging and Surveillance in Seminoma Testis (TRISST) provided evidence to support less frequent imaging for patients with CSI seminoma and the potential to use magnetic resonance imaging (MRI) instead of CT (20). This randomized trial demonstrated the non-inferiority of MRI compared with CT during the follow-up of patients with CSI seminoma, as well as the non-inferiority of 3 versus 7 radiologic assessments by cross-sectional imaging. Although there was an absolute increase of 2.5% in events with 3 versus 7 scans, the 5-year survival rate was excellent with 99% in all arms (20). Two critical considerations for the generalizability of these findings are that: (I) adherence to timely scan completion in this trial was considerably higher than that of routine practice, and (II) the availability of high-quality MRIs in the community read by radiologists who have experienced with testicular GCT. Cost and patient satisfaction with MRI (including claustrophobia with closed MRI and time required for the study) will also need to be considered. Ultimately, the advent of more specific STMs may help shift strategies that use serum biomarkers to detect relapsed disease followed by imaging as a confirmatory diagnostic tool to more effectively avoid the use of imaging with ionizing radiation.

De-implementing use of non-guideline recommend imaging studies is another important consideration in reducing the cost and burden of diagnostic pursuit in men with early-stage testicular cancer. For example, the diagnostic utility of ^{18}F-fluoro-deoxy-glucose positron emission tomography-computed tomography (^{18}F-FDG-PET-CT) was less promising once disseminated into

routine clinical practice. Although ^{18}F-FDG-PET-CT may offer helpful high negative-predictive value (21), the low positive predictive value may be misleading; therefore, the only guideline-endorsed use of ^{18}F-FDG-PET-CT is in restaging patients with metastatic seminoma who had post-chemotherapy residuals >3 cm 6–8 weeks following completion of systemic treatment (22).

miRNA

In patients with CSI GCT, up to 97% of seminomas and 60% of NSGCT recur on surveillance without marker elevation (23). Accordingly, surveillance schedules for these patients require approximately 6–10 axial imaging scans within the first 5 years after diagnosis, resulting in associated costs, patient inconvenience, and ionizing radiation exposure (20). A more sensitive circulating biomarker of relapse could help to guide a risk-adapted surveillance strategy, and thus potentially decrease the number of axial imaging tests required or completely obviate the need for routine cross-sectional imaging. Over the last decade, a panel of GCT-specific miRNAs have been described, which are overexpressed in GCT tissue (except teratoma) and measurable in the blood. Among these miRNAs, circulating miR-371a-3p has the strongest performance characteristics, with the bulk of data derived from the pre-orchiectomy setting and at the time of macroscopic relapse (24).

Several groups have also examined the diagnostic accuracy of circulating miR-371a-3p to detect occult metastases or early relapse in patients with CSI GCT. In the largest study to date, presence of serum miR-371a-3p after orchiectomy was associated with 83% sensitivity and 96% specificity for identifying relapses (24). These results were corroborated in a cohort of 25 patients with CSI disease whereby a circulating miR-371a-3p test correctly identified all patients who ultimately had a recurrence (1/25) and those who did not (24/25) (25). Lafin *et al.* demonstrated that serum miR-371a-3p accurately detected minimal residual pathologically confirmed viable GCT at chemotherapy-naive retroperitoneal lymph node dissection (26). In this 24-patient cohort with normal conventional STMs, miR-371a-3p showed a 100% sensitivity and 92% specificity, demonstrating the value of circulating miRNAs in this setting.

While these data are encouraging, circulating miRNA levels are associated with tumor mass, raising concerns about whether they are detectable in occult metastases (24). A recent report indicates that miR-371a-3p levels following orchiectomy do not predict relapse but become measurable at the time of clinical relapse in 94% of cases (27). Another study found that circulating miR-371a-3p levels detect recurrences at a median of 2 months earlier than standard follow-up investigations (28). However, continued refinement of the assay may be needed to overcome current sensitivity limitations for earlier detection of occult metastases. Two ongoing large-scale prospective studies (NCT04435756 and NCT04914026) will further inform the performance of miR-371a-3p for temporal detection and pattern of relapse in patients with CSI disease. Importantly, these studies may provide insight on whether treatments could potentially be de-escalated (i.e., locoregional therapy *vs.* systemic therapy) if a relapse were detected earlier based on miR-371a-3p status versus conventional imaging and STMs.

The potential future role and impact of circulating miR-371a-3p in surveillance and monitoring of patients with CSI GCT is profound. A potential example is that for patients with pure seminoma, cross-sectional imaging may be reserved for patients suspected of a relapse based on detectable circulating miR-371a-3p. However, for patients with NSGCT, serum miR-371a-3p holds promise for identifying viable GCT elements but axial scans cannot be entirely omitted given our current inability to detect pure teratoma with either miR-371a-3p or other circulating biomarkers (29). Ultimately, in the future, the frequency of cross-sectional imaging may potentially be safely decreased for patients with CSI NSGCT. Although outstanding issues related to the assay cutoff values, interpretation, and reproducibility do exist, circulating miR-371a-3p may potentially transform surveillance programs for patients with early-stage GCTs with a tremendous reduction on cost, need for axial imaging, and patient inconvenience.

Conclusions

There are growing evidence and need for alternative approaches to the traditional fixed surveillance schedule paradigm for patients with early-stage testicular cancer, which includes frequent surveillance CT scans and STM tests. The explosion of telehealth platforms and their use provides an opportunity to reduce the burden of travel and time for patients. Additional research on how new diagnostic approaches, including miRNA as an STM and alternative surveillance schedules, will be implemented are necessary to ensure that there is no compromise in the ability to detect relapse, particularly in the first two years of surveillance when patients are at greatest risk.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the wok are appropriately investigated and resolved.

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