Minerva Urologica e Nefrologica
EDIZIONI MINERVA MEDICA

Analysis of clinical utility of abdominopelvic computer tomography in the follow up of Stage I Seminoma. A single center evaluation.

Michele RIZZO, Luca ONGARO, Francesco CLAPS, Dario GHASSEMPOUR, Enrica VERZOTTI, Francesca MIGLIOZZI, Matteo BOLTRI, Nicola PAVAN, Giulio GARAFFA, Stefano BUCCI, Paolo UMARI, Carlo TROMBETTA, Giovanni LIGUORI

Minerva Urologica e Nefrologica 2019 Dec 11
DOI: 10.23736/S0393-2249.19.03562-8

Article type: Original article

Article first published online: December 11, 2019
Manuscript accepted: November 5, 2019
Manuscript revised: October 25, 2019
Manuscript received: July 4, 2019

Analysis of clinical utility of abdominopelvic computer tomography in the follow up of Stage I Seminoma. A single center evaluation.

Michele RIZZO [1*], Luca ONGARO [1], Francesco CLAPS [1], Dario GHASSEMPOUR [1], Enrica VERZOTTI [1], Francesca MIGLIOZZI [1], Matteo BOLTRI [1], Nicola PAVAN [1],Giulio GARAFFA [2], Stefano BUCCI [1], Paolo UMARI [3], Carlo TROMBETTA [1], Giovanni LIGUORI [1]

[1] Urologic Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy; [2] The Institute of Urology, University College London Hospitals, London, UK; [3] Urologic Clinic, Department of Surgery, University of Eastern Piedmont, Novara, Italy

*Corresponding author: Michele Rizzo M.D., Urologic Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, 34149, Trieste, Italy. E-mail: mik.rizzo@gmail.com

ABSTRACT

BACKGROUND:

Abdominopelvic computer tomography (CT) is widely used in the follow up of seminoma patients after radical orchidectomy. The aim of this study is to evaluate the clinical utility of abdominopelvic computer tomography in the follow-up of patients with Stage I seminoma.

METHODS:

The pathological reports of all patients that have undergone radical orchidectomy in our tertiary referral center between January 2002 and January 2018 have been retrospectively reviewed. All patients with Stage I seminoma and negative serum tumor markers after radical orchidectomy were included. Patients with follow-up shorter than 12 months were excluded. Surveillance records of every patient were reviewed with particular regard to abdominopelvic imaging.

RESULTS:

Of the 133 patients who have undergone radical orchidectomy in our center, 55 had stage I pure seminoma with normal levels of serum tumor markers after surgery. Two patients were excluded as the follow-up was inadequate. Mean follow-up was 63,2 months (IQR: 30-73). The results of 211 abdominopelvic CTs performed as part of the follow up were reviewed. Two (3,7%) patients developed recurrence; one consisted of a scrotal lump and was diagnosed with ultrasonography (US) while the second appeared as paraaortic nodal metastasis and was diagnosed with abdominopelvic CT. The recurrence was successfully treated in both patients. A single abdominopelvic CT was useful for the detection of recurrent disease in our entire study population. No cancer specific death has been reported in the study population.

CONCLUSIONS:

Follow-up schedules for stage I seminoma exposes patients to potential risks of radiation-induced tumors, emotional distress and represent a significant burden for the healthcare system. The current series suggests that a better risk adapted patient-tailored follow-up program is needed in order to avoid unnecessary investigations.

Key words: Seminoma, Computer Tomography, Recurrence, Testis Cancer

TEXT

Introduction

Testicular cancer represents 1% of all male neoplasms with an estimated incidence of three to ten new cases every year per 100,000 men in the Western World. Around 90-95% of testis neoplasms are germ cell tumors and about 50% of these are seminomas [1-2]. Large population-based studies show that Stage I accounts for 75-80% of all seminomas [3]. As stated in the 2009 TNM edition, Stage I comprehends locally confined and locally advanced tumors, with or without elevation of serum testicular tumor markers and without nodal involvement and distant metastasis [4]. According to European Association of Urology (EAU) guidelines, all patients surgically treated for Stage I pure seminoma should routinely undergo physical examination, tumor markers assessment and abdominopelvic Computer Tomography (CT) scans on regular set intervals in order to early detect recurrences. Regarding abdominal imaging, practice guidelines recommend repeating abdominopelvic CT scans every six months for the first 2 years after surgery and then, if all investigations fail to demonstrate any recurrence, at 36 and 60 months [5]. Patients with organ confined pure seminoma are generally young men with good prognosis and long-life expectancy, as relapses are rare in this category [6]. Surveillance is mandatory, but schedules currently proposed by practice guidelines are based on low level evidence where the benefits of very strict follow-up in all patients with Stage I pure seminoma has not been clearly demonstrated. In this scenario, the risks related to ionizing radiation exposure in patients undergoing repeated CT scans represent a clinical concern and may well outweigh the benefits.

Currently recommended follow up schedules including 6 monthly abdominopelvic CT scans for Stage I seminoma could potentially expose patients with long life expectancy to unnecessary radiation exposure without any demonstrated clear benefit in terms of recurrence detection and overall survival.

Aim of the current study is to evaluate the clinical utility of abdominopelvic CT during follow-up of patients that have previously undergone radical orchidectomy for Stage I pure seminoma in our tertiary referral center.

Materials and methods

The present study has been conducted in accordance with the ethical standards of the Helsinki declaration and its later amendments. Local Ethical Committee approval was not required due to the retrospective design of this study and to the fact that procedures were performed according to internal policies and international guidelines recommendations. All patients enrolled were provided with an informed consent and all data were managed anonymously. This article does not contain any studies with animals performed by any of the authors.

The histopathology of all patients that have undergone radical orchidectomy between January 2002 and January 2018 in our tertiary referral hospital was retrospectively reviewed. All Stage I pure seminomas with postoperative normal level of α-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) were included in the study. Patients with postoperative follow-up shorter than 12 months were excluded from this series. All clinical notes were retrospectively reviewed with particular emphasis to the reason of referral, pathological features as presence of germ cell neoplasia in situ (GCNIS), rete testis, epididymis, tunica vaginalis and spermatic cord invasion, pre and post-operative clinical examination, serum tumor markers and finally chest and abdominopelvic imaging. Histopathology was assessed by our dedicated uro-pathologist team. Follow-up protocol in our Institution was in line with contemporary recommendations and included periodic clinical evaluation and assessment of serum tumors markers levels every 3 months for the first 2 years and annually thereafter. An abdominopelvic CT scan was carried out every 6 or 12 months for the first 2 years and then annually. The presence of lung secondary lesions was ruled out with a chest CT scan or with plane X Ray based on clinical decision. Every single abdominopelvic CT, chest CT and chest X-ray were evaluated to specifically assess

the utility of all abdominopelvic imaging performed for oncological follow-up purpose in this cohort of patients. Adjuvant treatments, recurrences and salvage treatment, cancer related mortality and overall mortality were also evaluated. Statistical analysis was performed with IBM ® SPSS Statistics ® 24.0 version.

Results

Overall, 133 orchiectomies for suspected testis malignancies were performed. Sixty-six cases were classified as pure seminoma at histopathology and 55 of these were stage I with normal levels of serum tumor markers after radical orchidectomy. Two patients were excluded because their follow-up was shorter than 12 months. The remaining 53 patients (96.36%) were enrolled into the study. Patient characteristics and histopathology are shown in Table 1. Mean age at the time of surgery was 37,53 years (Interquartile Range IQR=31-44). Forty-six (86,8%) cases were Stage IA and 7 (13,2%) were Stage IB seminoma. Diagnosis of testis neoplasm was made after the detection of a scrotal lump at self-examination in 29 (54,71%) patients. Malignancy was identified following investigations for scrotal pain in 9 (16,98%) and for infertility in 3 (5,66%). Malignancy was incidentally found in 4 (7,55%). Data about testis tumor presentation were not available in the remaining 8 (15,1%) patients (Figure 1). Tumor was found in the left testis in 56,6% of patients and in the right one in the remainder. One patient who had previously undergone left radical orchidectomy at the age of 33 years for a Stage I pure seminoma underwent right radical orchidectomy for a metachronous Stage I seminoma at the age of 45. Given the history of this particular patient, the seminoma of the right testis was not considered as a recurrence but as a metachronous tumor. TNM pathological stage was pT1 in 45 (84,9%) patients pT2 in 6 (11,32%) and pT3 in 2 (3,77 %). Tumor diameter was greater than 4 cm in 21 patients (39.6%). Rete testis invasion was detected in 6 cases (10.9%). One patient with pT1a pure seminoma presented a multifocal neoplasm in the testis parenchyma. GCNIS was documented in 45 (84,9%) orchidectomy specimens. Fourteen patients received adjuvant chemotherapy, 11 adjuvant radiotherapy and 28 patients underwent active surveillance. Mean follow-up was 63,2 months (IQR: 30-73).

From the review of the clinical notes it appeared that a total of 211 abdominopelvic CT scans, 111 chest CT scans and 226 chest x-rays were performed on the entire cohort for oncologic surveillance. Mean cumulative exposure to ionizing radiation due only to abdominopelvic CT was 62,47 mSv (+/- 10%) during the whole follow up period.

During the study period 2 (3,77%) recurrences were detected (patient 1 and patient 2).

Patient 1 was a 35 years old man with previous history of undescended testis. In 2012 he had undergone right radical orchidectomy after ultrasonographic finding of a testicular mass. Preoperative serum tumor markers (HCG and LDH) were above the normal range. No signs of metastasis were reported at staging abdominopelvic and chest CT scans. Histopathology revealed a pT1, multifocal seminoma with 2 tumors, the larger measuring 3 cm in diameter, and presence of GCNIS. Serum tumor markers returned in the normal range 1 month after surgery. Twenty-two months later an abdominopelvic CT scan revealed enlarged para-aortic nodes compatible with recurrence. Rise of serum tumor markers was also detected. The patient remains tumor free 52 months after completing his cycles of chemotherapy.

Patient 2 had undergone radical orchiectomy at the age of 43 years after ultrasonographic finding of a left testicular mass 10 cm in diameter. LDH was elevated while AFP and HCG were in the normal range. Preoperative chest x-ray and abdominopelvic CT scan failed to demonstrate any secondary lesion; histopathology demonstrated a pT3 seminoma with massive necrotic component, involvement of the intercrural fascia and lymphatic invasion in the proximal tract of the spermatic cord. Three months later, a new left scrotal lump, which proved to be a seminoma, was surgically removed and the patient subsequently underwent adjuvant radiotherapy. The patient remains disease-free 25 months after completing the adjuvant radiotherapy.

No seminoma related deaths were reported in the cohort. One patient died due to a Non-Hodgkin lymphoma 5 years after his radical orchidectomy. The 52 remaining patients of this study were alive and disease free at the last follow-up.

Discussion

The main finding of the current study is that only 0,47% of all abdominopelvic CT scans performed has been useful to identify retroperitoneal relapse. Given this result, it appears that abdominopelvic surveillance has not been beneficial in 99,55% of all patients. Previous

studies demonstrated that relapses of Stage I seminoma can be effectively treated with disease free survival rates higher than 90% at 10 years after salvage therapy [7]. Given this well-established evidence, utility of relapse diagnosis is unquestionable and surveillance of patients in this category is mandatory. The goal of follow-up programs proposed by internationals guidelines is to identify asymptomatic relapses in an early and oligometastatic stage in order to maximize the chances of success while minimizing the aggressiveness of treatments [5]. It is also well established that most of seminoma relapses occur within the first 2 years after the initial radical orchidectomy and therefore a very strict follow-up during this period is recommended [8]. However, evidences sustaining clinical benefits of present surveillance schedules for patients with Stage I pure seminoma are poor [9]. Remarkably, Stage I encompasses a wide range of malignancies, from small masses confined to the testis that don't involve the tunica albuginea or the rete testis, to large tumors that invade the scrotum [4]. Heterogeneity of the neoplasms that are currently classified as Stage I testicular seminomas is a possible explanation for the difference in the recurrence rates reported in various studies. It is reasonable that follow-up programs could be tailored according to a more precise estimation of relapse risks. Previous studies tried to identify predictors of recurrence. In a population of 1118 patients with Stage I seminoma, Tandstad et al reported a recurrences rate of 6,7% at mean follow-up of 5,6 years. Stromal invasion of the rete testis and tumor diameter >4cm were identified as independent risk factors for recurrence. In the subgroup without risk factors the recurrence rate was 4.0% for patients managed by surveillance alone and 2.2% for patients that underwent adjuvant chemotherapy with carboplatin. In patients with one or two risk factors the recurrence rate was 15.5% in the subgroup managed by surveillance only and 9.3% in those managed with adjuvant carboplatin [10]. Similarly, Warde et al in 2002 identified dimension >4cm and rete testis invasion as independent risk factors of recurrence. These Authors found that 5 years recurrence rate was 13% for tumors <4cm and 24% for tumors >4cm. Recurrence rates in patients with and without rete testis invasion were respectively 14% and 24% [11]. So far, the recurrences rate of Stage I seminoma is not well established and is generally higher in older studies. Recently Tyrrell et al presented a series of 501 patients with Stage I pure seminoma. In their series, relapses occurred in 6,2% of patients who received adjuvant treatment and in 6,1% of the patients in the surveillance group [6]. Data on the precise location of recurrences are lacking in many studies. Considering that some relapses are diagnosed by clinical examination, scrotal ultrasound or following the elevation of serum tumors markers, it is

reasonable to affirm that abdominopelvic CT scan is not useful for the diagnosis of all relapses. Considering that less than 10% of patients treated for Stage I seminoma do relapse, it seems that 90% of patients in this category at least undergo 4 useless abdominopelvic CT in the first 2 years after radical orchidectomy. In the current series, 1 recurrence occurred into the scrotum and has been diagnosed during physical examination. Given the young age of men diagnosed with testis cancer and their long-life expectancy the risk connected to ionizing radiation exposition due to radiologic surveillance represents a clinical concern. This is because the range of radiation dose administered for an abdominal CT scan is about 15 millisieverts (mSv) in adult and the evidence derived from epidemiologic studies shows that radiation dose in the range between 30 to 90 mSv increases the risk of radiation induced tumors [12]. Other Authors showed that a single abdominal CT performed in 20-year-old man leads to a radiation-induced cancer in 1 on 660 cases [13]. Moreover, repeated CT scans could determine an increase of cumulative risk of developing a radiation-induced malignancy. In the current series, more than 99% of all the CT scans performed for surveillance purpose were unnecessary and therefore we are questioning the real utility of recommending 4 abdominopelvic CT during the first 24 months after radical orchidectomy to all patients with Stage I seminoma. The current series suggests that the current follow up protocol for patients with stage I seminoma may be excessive. This concept has been already previously highlighted by various Authors. In particular, Lehnich et al. showed a diffuse concern among physicians regarding secondary malignancies due to follow up related radiation exposure. This fact led, in combination with unfamiliarity of physicians with guidelines, to an underuse of CT scans not compensated by alternative imaging modalities [14]. Other Authors instead demonstrated an equal underuse and overuse of CT scan, with the risk of missing a relapse in the first case and of unnecessary and potentially detrimental radiation exposure in the second[15]. We believe that surveillance is mandatory but probably follow-up programs could be tailored to reduce the risks connected to the ionizing radiation exposition. In an attempt to reduce ionizing radiation exposure during follow up, magnetic resonance (MRI) could be used instead of CT, as stated in 2018 by ESMO Consensus Conference on testicular germ cell cancer [16]. Although in the hands of an expert sonographer testicular ultrasound (US) might also be alternated to CT scans to screen the retro-peritoneum during follow-up in order to minimize radiation exposure, especially in patients with no risk factors, at the time US is not recommended as assessment tool of regional lymph nodes since CT and, in experienced centers, MRI remain the primary modality used to monitor testicular

seminoma [17]. Psychological aspects should also be considered in the management of these patients. Previous studies showed that men treated for testis cancers experience mild psychological distress and impaired quality of life [18]. Since strict follow-up with invasive examinations could worsen the psychological distress, tailoring surveillance program could reduce this source of anxiety. Since primary chest recurrences are almost absent in patient with stage I seminoma and since reliable serum tumor markers and in proper cases CT scan can early detect chest recurrences[19], chest surveillance for patients in this category is not routinely recommended by guidelines [5,16]. In our analysis no chest X-ray and chest CT has been useful to detect relapse. The main limitations of the present study came from the retrospective design and the small number of patients enrolled as consequence of the inclusion criteria: a wider cohort, possibly in a multicentre trial context, is needed to draw more solid conclusions. Strengths of the present study are the long duration of mean follow-up, the very low rate of drop (3,77%) and the large number of abdominopelvic CT scans analyzed.

Conclusions

Stage I accounts for the most of the patients diagnosed with seminoma. Surveillance is mandatory, but common follow-up schedules expose patients to life-long risks connected with ionizing radiations. Although the results of this study should be interpreted with caution due to its retrospective nature and the small number of patients enrolled, it clearly suggests that current follow-up schedules may represent a significant overtreatment and support the need of designing new follow-up programs based on actual risk of recurrence in order to avoid unnecessary exams.

REFERENCES

1. Rosen A, Jayram G, Drazer M, Eggener SE. Global trends in testicular cancer incidence and mortality. Eur Urol 2011; 60: 374-9.

2. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine (Baltimore) 2018; 97: e12390.

3. Klepp O, Flodgren P, Maartman-Moe H, Lindholm CE, Unsgaard B, Teigum H et al. Early clinical stages (CS1, CS1Mk+ and CS2A) of non-seminomatous testis cancer. Value of pre - and post-orchiectomy serum tumor marker information in prediction of retroperitoneal lymph node metastases. Swedish-Norwegian Testicular Cancer Project (SWENOTECA). Ann Oncol 1990; 1: 281-8.

4. Brierley JD, Gospodarowicz MK, Wittekind C. The TNM Classification of Malignant Tumours 8th edition 2016.

5. Albers P, Albrecht W, Algaba F, C. Bokemeyer, G. Cohn-Cedermark, K. Fizazi et al. EAU Guidelines on Testicular Cancer. © European Association of Urology 2018. Available from: http://uroweb.org/guideline/testicular-cancer 2018.

6. Tyrrell HEJ, Church DN, Joseph J, Traill ZC, Sullivan ME, Tuthill MH et al. Changing Practice Evaluation-Stage 1 Seminoma: Outcomes With Adjuvant Treatment Versus Surveillance: Risk Factors for Recurrence and Optimizing Follow-up Protocols-Experience From a Supraregional Center. Clin Genitourin Cancer 2018; 16: 240-4.

7. Aparicio J, Maroto P, del Muro XG, Gumà J, Sánchez-Muñoz A, Margelí et al. Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. J Clin Oncol 201; 129: 4677-81.

8. Oldenburg J, Horwich A; ESMO Guidelines Committee. Appendix 9: Testicular seminoma and non-seminoma: eUpdate published online 29 June 2017 (www.esmo.org/Guidelines/Genitourinary-Cancers). Ann Oncol 2017; 28: iv165-6.

9. Rustin GJ, Mead GM, Stenning SP, Vasey PA, Aass N, Huddart RA et al. Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council

Trial TE08, ISRCTN56475197--the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol 2007; 25: 1310- 5.

10. Tandstad T, Stahl O, Dahl O, Haugnes HS, Håkansson U, Karlsdottir Å et al. Treatment of stage I seminoma, with one course of adjuvant carboplatin or surveillance, risk-adapted recommendations implementing patient autonomy: a report from the Swedish and Norwegian Testicular Cancer Group (SWENOTECA). Ann Oncol 2016; 27: 1299-304.

11. Warde P, Specht L, Horwich A, Oliver T, Panzarella T, Gospodarowicz M et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002; 20: 4448-52 .

12. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007; 357: 2277-84.

13. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, Gould R et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 2009: 169: 2078-8.

14. Lehnich AT, Rusner C, Chodick G, Katz R, Sella T, Stang A. Actual frequency of imaging during follow-up of testicular cancer in Israel-a comparison with the guidelines. Eur Radiol. 2019; 29:3918-926

15. Nestler T, Baunacke M, Dräger D, von Landenberg N, Groeben C, Huber J. Testicular cancer guideline adherence and patterns of care in Germany: A nationwide survey. Eur J Cancer Care (Engl) 2019; 28 :e12917

16. Honecker F, Aparicio J, Berney D, Beyer J, Bokemeyer C, Cathomas R et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol. 2018; 29:1658-686.

17. Hale GR, Teplitsky S, Truong H, Gold SA, Bloom JB, Agarwal PK. Lymph node imaging in testicular cancer. Transl Androl Urol. 2018; (7):864-74.

18. Smith AB, Butow P, Olver I, Luckett T, Grimison P, Toner GC et al. The prevalence, severity, and correlates of psychological distress and impaired health-related quality of life following treatment for testicular cancer: a survivorship study. J Cancer Surviv 2016: 10: 223-33.

19. De La Pena H, Sharma A, Glicksman C, Joseph J, Subesinghe M, Traill Z et al. No longer any role for routine follow-up chest x-rays in men with stage I germ cell cancer. Eur J Cancer. 2017; 84:354-59

NOTES

Conflicts of interest.

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

Funding.

The present study did not receive subsidies.

Authors' contributions.

M. Rizzo: project development, data collection, data analysis, manuscript writing

L. Ongaro: data collection, manuscript writing

F. Claps: manuscript editing

D. Ghassempour: data collection

E. Verzotti: manuscript editing

F. Migliozzi: manuscript editing

M. Boltri: manuscript editing

N. Pavan: manuscript editing

G. Garaffa: manuscript writing

S. Bucci: manuscript editing

P. Umari: manuscript editing

C. Trombetta: manuscript reviewing

G. Liguori: manuscript reviewing

Congresses.

Congresso nazionale SIA - Bari 2019, 23rd – 25th May 2019, Bari, Italy

68° Convegno SUNI - Finalborgo, 10th – 11th May 2019, Finalborgo, Italy

TABLES

Table I.— Patients preoperative and pathological characteristics

Characteristics	No	%
Age (mean)		
<35	25	47
>35	28	53
Pre-orchiectomy serum hCG[1]		
Elevated	14	26,4
Not elevated	39	73,6
Pre-orchiectomy serum AFP[2]		
Elevated	0	0
Not elevated	53	100
Pre-orchiectomy serum LDH[3]		
Elevated	6	11,3
Normal	47	88,7
Dimension		
< 4cm	32	60
> 4cm	21	39.6
Rete testis invasion		
Presence	6	11
Absence	47	89
pT		
pT1	45	85
pT2	6	11,3
pT3	2	3,7
pT4	o	0
Stage		
Stage IA	46	86,8
Stage IB	7	13,2

hCG[1]: human chorionic gonadotropin, AFP[2]: Alpha-fetoprotein, LDH[3]: Lactate dehydrogenase

TITLES OF FIGURES

Figure 1.— Clinical presentations of testis cancer