Prognosis of Testicular Germ Cell Tumors: Experience from the Medical Oncology Department of Hassan II Hospital in Fez and a Review of the Literature

Introduction :

Testicular neoplasms are the most common solid organ malignancies in men aged 15 to 35 years, accounting for 0.5% to 1% of all male cancers. Despite their relatively low incidence, these tumors are notable for their exceptionally high five-year survival rates, exceeding 90% in most cases (1) (2) (3) (4). Germ cell tumors of the testis (GCTTs), which constitute 98% of testicular cancers, are characterized by unique biological and clinical features. They are rare, with an annual incidence of 8 to 10 cases per 100,000 men in Northern European countries (5) (6), and exhibit a distinct peak in young men aged 20 to 45 years (7) (8).

GCTTs are histologically diverse, encompassing a spectrum of subtypes with varying clinical behaviors and therapeutic responses. They are broadly classified into two main groups: pure seminomas and non-seminomas. Non-seminomas include four pure histological subtypes—embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma—as well as mixed forms (9) (10). While seminomas and non-seminomas are traditionally thought to occur in equal proportions, recent studies suggest a rising incidence of seminomas (11). Notably, the presence of teratoma, a subtype resistant to both radiotherapy and chemotherapy, often necessitates tailored therapeutic approaches. Despite its frequent identification in pathological evaluations, teratoma is rarely highlighted in clinical series, underscoring a gap in the literature.

Clinically, GCTTs are distinguished by their reliance on serum biomarkers—alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH)—for diagnosis, staging, and treatment planning (9). Non-seminomas, in particular, are more likely to present with metastatic dissemination compared to seminomas, further complicating their management (12). Additionally, factors such as patient age, primary tumor size, pathological stage (pT), and biomarker levels play critical roles in risk stratification and therapeutic decision-making. However, the interplay between these factors remains poorly understood, as most studies have focused on isolated parameters or small cohorts, often derived from 20th-century data (13).

Despite the high cure rates associated with GCTTs, morbidity and mortality remain closely tied to the stage at diagnosis. Advanced disease is associated with poorer outcomes, increased treatment-related toxicity, and a higher risk of recurrence and death. These challenges highlight the need for ongoing research to refine risk stratification and optimize therapeutic strategies.

This study presents a retrospective analysis of 48 patients treated for testicular germ cell tumors at the Medical Oncology Department of Hassan II University Hospital in Fez, Morocco, between 2017 and 2024. Our objective is to describe the prognosis, treatment outcomes, and clinical characteristics of these patients, contributing to the growing body of evidence on GCTT management in low- and middle-income countries.

Material and methods :

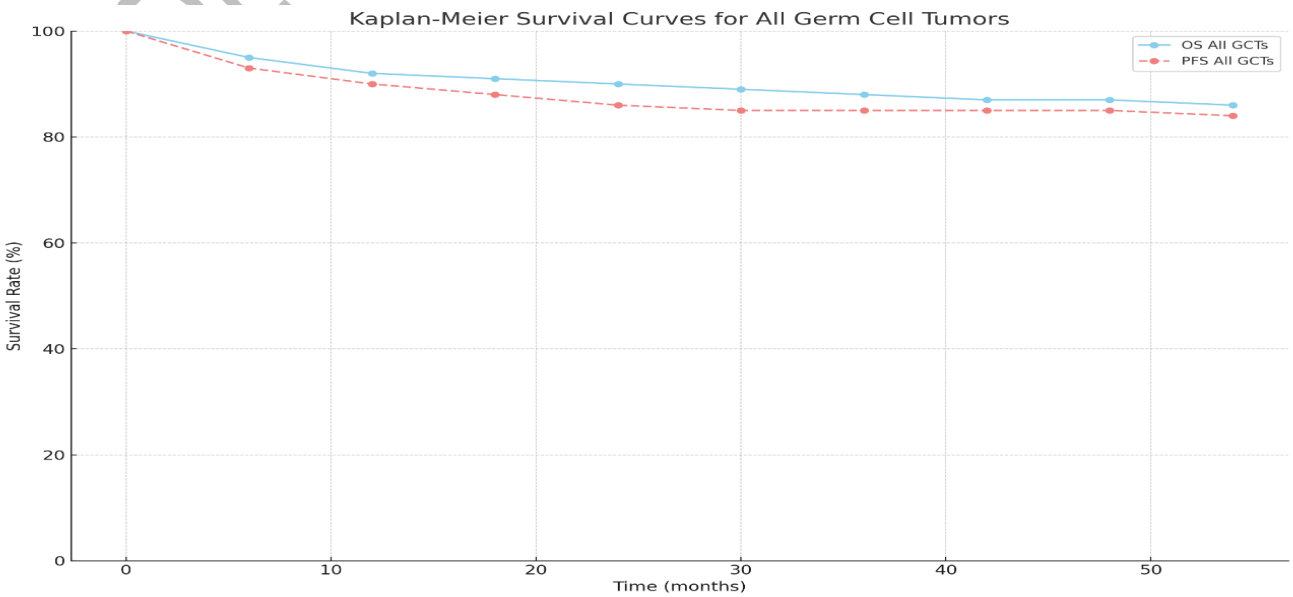
This retrospective study analyzed the medical records of 48 patients treated for testicular germ cell tumors at the Medical Oncology Department of Hassan II University Hospital in Fez, Morocco, between January 2017 and September 2024. Data were extracted from digitized medical records and analyzed using SPSS software (version 20).

Results :

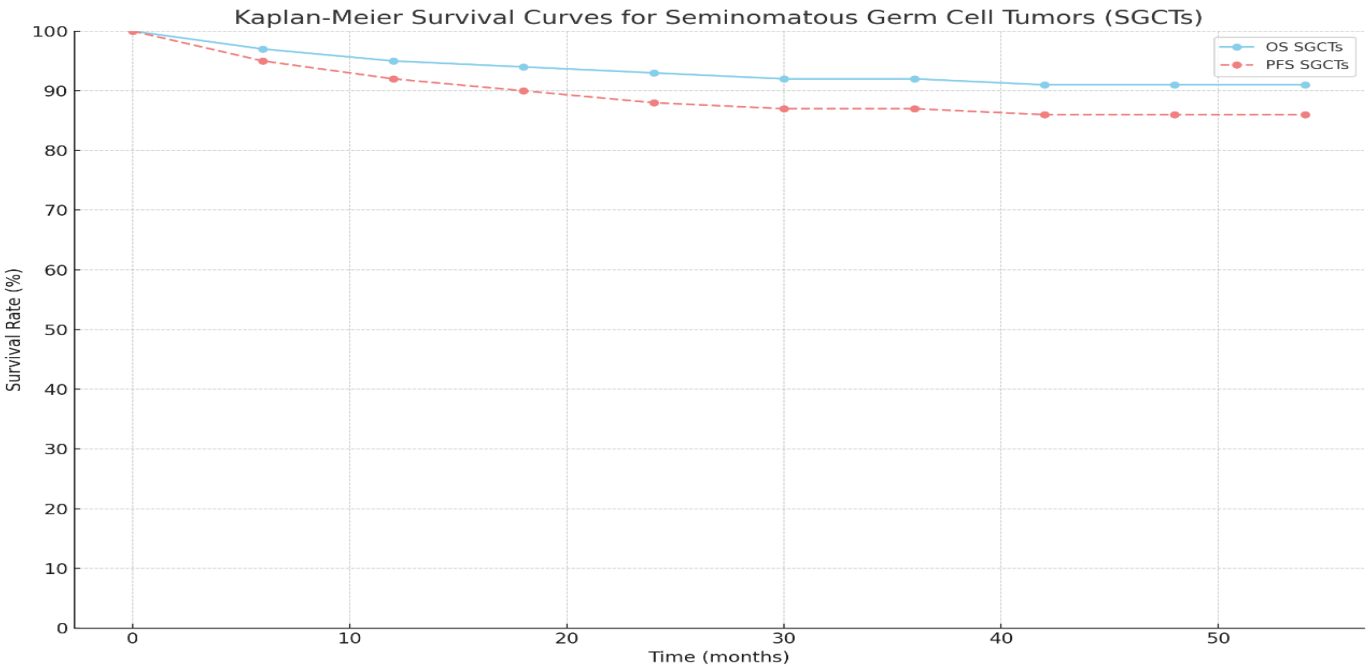
The annual incidence rate was estimated at 6 new cases per year. The mean age of the patients was 32 years (range: 15–61 years). Cryptorchidism was the most common risk factor, present in 31.25% of patients, while scrotal swelling was the most frequent clinical symptom, observed in 80% of cases. Diagnosis was confirmed through orchiectomy in all patients (100%). Disease stages at diagnosis were distributed as follows: stage I (16%), stage II (10%), and stage III (22%). According to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification, 68% of seminomatous germ cell tumor (SGCT) patients had a favorable prognosis, while 32% had an intermediate prognosis. In contrast, 50% of non-seminomatous germ cell tumor (NSGCT) patients had an unfavorable prognosis.

The BEP regimen (Bleomycin, Etoposide, Cisplatin) was the most commonly used first-line treatment, achieving complete remission in 31.25% of patients and partial response in 12.6%. Disease progression occurred in 18.8% of cases (n = 9), necessitating second-line chemotherapy: six patients received the TIP protocol, two received BEP, and one received VIP. Additionally, three patients underwent surgery for residual masses, and two received palliative radiotherapy for brain metastases. Six deaths were reported, all in stage III patients (three SGCT and three NSGCT).

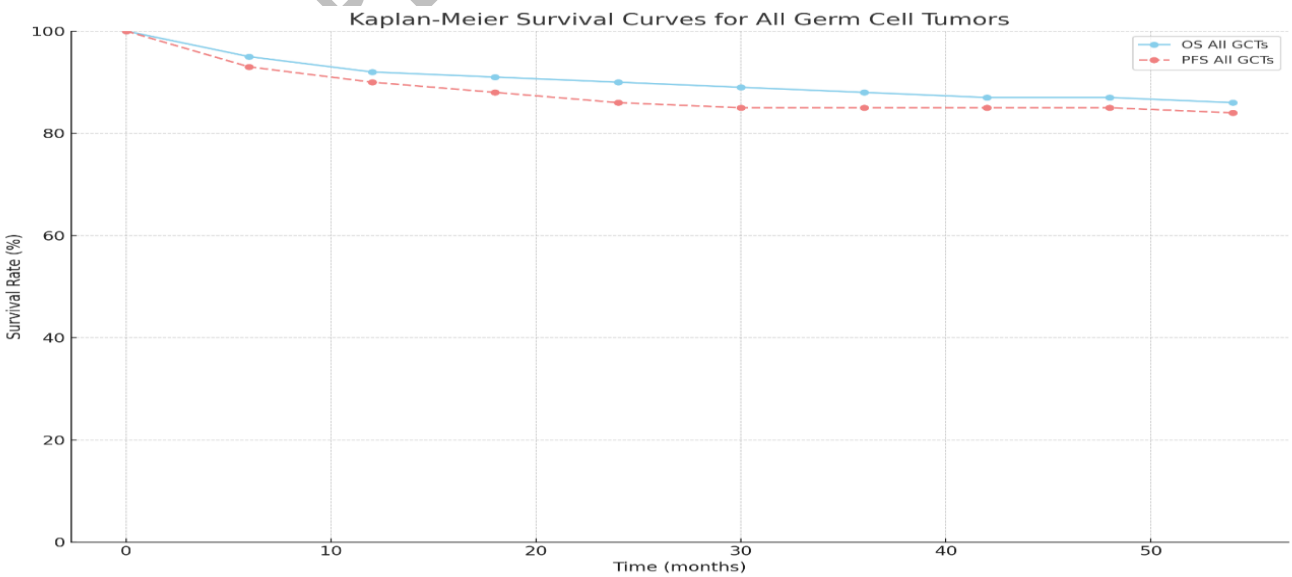
After a median follow-up of 4 years, the overall survival (OS) rate was 90%, and the progression-free survival (PFS) rate was 60% across all histologies. SGCTs demonstrated superior outcomes, with OS and PFS rates of 91% and 86%, respectively, compared to NSGCTs, which had OS and PFS rates of 85% and 80%.



Graphic 1: Kaplan-Meier curves for overall survival and progression-free survival of all Germ Cell Tumors



Graphic 2: Kaplan-Meier curves for overall survival and progression-free survival of all Seminomatous Germ Cell Tumors



Graphic 3: Kaplan-Meier curves for overall survival and progression-free survival of all Seminomatous Germ Cell Tumors

Discussion :

Epidemiological and clinical insights:

Testicular germ cell tumors (TGCTs) are rare malignancies, accounting for 1–1.5% of all male cancers, yet they represent the most common solid tumors in young men aged 15–35 years (14) (15). In our study, the annual incidence of TGCTs at Hassan II University Hospital of Fez was 6 new cases per year, reflecting the rarity of this disease. This is lower than the incidence reported in studies from Northern Europe and Japan, where annual rates range from 8 to 10 cases per 100,000 men (16). The median age of our patients was 32 years, consistent with global data, though slightly younger than the median age of 37 years reported in Japanese cohorts (17). This discrepancy may reflect demographic or regional differences in disease presentation.

Scrotal swelling (80%) and pain (30%) were the most common presenting symptoms, aligning with findings from Bosl et al., who reported that 87.5% of patients present with testicular-related symptoms (18). Delays in diagnosis, often due to patient reluctance or lack of awareness, remain a significant challenge, as they can lead to advanced disease at presentation. This underscores the need for public health initiatives to improve early detection and reduce diagnostic delays.

Pathological and Staging Characteristics:

In our cohort, seminomatous germ cell tumors (SGCTs) accounted for 58.3% of cases, while non-seminomatous germ cell tumors (NSGCTs) represented 41.7%. This distribution differs slightly from global trends, where NSGCTs are typically more prevalent (19). The higher proportion of SGCTs in our series may reflect regional variations in tumor biology or diagnostic practices.

Staging revealed that 16% of patients presented with stage I disease, 10% with stage II, and 22% with stage III. Notably, a significant proportion of patients were diagnosed at advanced stages, contrasting with Japanese series where stage I disease is more common . This highlights potential gaps in early diagnosis and access to care in our setting. According to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification, 68% of SGCT patients had a favorable prognosis, while 50% of NSGCT patients had an unfavorable prognosis, consistent with the more aggressive nature of NSGCTs.

Therapeutic outcomes and comparisons:

The cornerstone of TGCT management remains inguinal orchiectomy, performed in all our patients, followed by risk-adapted chemotherapy or surveillance. The BEP regimen (Bleomycin, Etoposide, Cisplatin) was the most commonly used first-line treatment, achieving complete remission in 31.25% of patients and partial response in 12.6%. These outcomes align with global standards, where BEP chemotherapy is the gold standard for advanced TGCTs, with cure rates exceeding 90% in good-prognosis groups (20) (21).

For stage I seminoma, active surveillance was employed in 3 patients, while 6 received adjuvant carboplatin. This approach is supported by both the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU), which recommend surveillance as the preferred option to minimize overtreatment, with adjuvant carboplatin reserved for patients seeking to reduce relapse risk (22) (23). In stage II and III seminoma, BEP chemotherapy demonstrated high efficacy, consistent with guidelines recommending 3 cycles for optimal outcomes (24).

In NSGCTs, treatment strategies were tailored to risk stratification. For stage I disease, active surveillance was used in low-risk patients, while high-risk patients received a single cycle of BEP. For advanced NSGCTs, 3–4 cycles of BEP or VIP (Vinblastine, Ifosfamide, Cisplatin) were administered, depending on prognostic category. These approaches are in line with international guidelines, which emphasize the importance of risk-adapted therapy to balance efficacy and toxicity (25) (26).

Survival outcomes:

After a median follow-up of 4 years, the overall survival (OS) rate was 90%, and progression-free survival (PFS) was 60% across all histologies. SGCTs exhibited superior outcomes, with OS and PFS rates of 91% and 86%, respectively, compared to 85% and 80% for NSGCTs. These findings are consistent with global data, where SGCTs demonstrate better survival due to their radiosensitivity and less aggressive behavior (27). The slightly lower PFS in NSGCTs reflects their propensity for metastatic spread and resistance to treatment in high-risk cases.

Radiotherapy and palliative care :

Radiotherapy was utilized in 2 patients with brain metastases for palliative purposes. While historically a mainstay in seminoma treatment, its role has diminished due to concerns about long-term toxicity, such as secondary malignancies and cardiovascular disease (28). Advances in radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and proton therapy, offer improved precision and reduced side effects, though their use remains limited to palliative settings in NSGCTs due to their lower radiosensitivity (29).

Sperm Preservation: (30)

Sperm abnormalities are prevalent in TGCT patients, affecting approximately 20% of cases. Chemotherapy and radiotherapy further exacerbate fertility issues, underscoring the importance of sperm cryopreservation before treatment. In our series, 3 patients underwent sperm preservation, a practice strongly recommended by international guidelines to safeguard reproductive potential . However, the low uptake in our cohort highlights the need for improved patient education and access to fertility preservation services.

Strenghts and limitations :

Our study provides valuable insights into the management and outcomes of TGCTs in a Moroccan population, contributing to the limited data from low- and middle-income countries (LMICs). However, the retrospective design and single-center nature of the study limit its generalizability. Additionally, the small sample size and relatively short follow-up period may affect the robustness of survival analyses. Future multicenter studies with larger cohorts and longer follow-up are needed to validate these findings.

Conclusion :

In conclusion, our study reaffirms the excellent prognosis of TGCTs, particularly SGCTs, when

managed according to international guidelines. The high survival rates observed in our cohort, even in advanced stages, underscore the effectiveness of modern therapeutic strategies, including risk-adapted chemotherapy and active surveillance. However, challenges such as delayed diagnosis, limited access to fertility preservation, and the need for tailored treatment approaches in high-risk NSGCTs remain areas for improvement. Continued research and adherence to evidence-based guidelines are essential to further enhance outcomes for patients with TGCTs.

Bibliography

1. *Nonseminomatous Testicular Tumors.* **Nauman M, Leslie SW.** s.l. : Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 33760513.

2. *Testicular cancer biomarkers: a role for precision medicine in testicular cancer.* **Leao R, Ahmad AE, Hamilton RJ.** s.l. : Clin Genitourin Cancer. 2018;S1558-7674.

3. *Updates in staging and reporting of testicular cancer.* **Magers MJ, Idrees MT.** s.l. : Surg Pathol Cancer. 2018;11:813-824.

4. *Testicular cancer.* **Cheng L, Albers P, Berney DM.** s.l. : Nat Rev Dis Primers. 2018;4:29.

5. *International variations and trends in testicular cancer incidence and mortality.* **Znaor A, Lortet-Tieulent J, Jemal A, Bray F.** s.l. : Eur Urol. 2014;65:1095–1106.

6. *Mortality of testicular cancer in east and west Germany 20 years after reunification: a gap not closed yet.* **Stang A, Bray F, Dieckmann KP, Lortet-Tieulent J, Rusner C.** s.l. : Urol Int. 2015;95:160–166.

7. *Testicular germ cell tumours.* **Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MA, Bokemeyer C.** s.l. : Lancet. 2016;387:1762–1774.

8. *Testicular cancer update. .* **Adra N, Einhorn LH.** s.l. : Clin Adv Hematol Oncol:2017;15:386–396.

9. *The 2016 who classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours.* **Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM.** s.l. : Eur Urol. 2016;70:93–105.

10. *Maintaining success, reducing treatment burden, focusing on survivorship: Highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer.* **Beyer J, Albers P, Altena R, Aparicio J, Bokemeyer C.** s.l. : Ann Oncol. 2013.

11. *National survey of patterns of care for testis cancer.* **Kennedy BJ, Schmidt JD, Winchester DP, Peace BL, Natarajan N, Mettlin C.** s.l. : Cancer. 1987;60:1921–1930.

12. *Treatment of a population based sample of men diagnosed with testicular cancer in the united states.* **Osswald M, Harlan LC, Penson D, Stevens JL, Clegg LX.** s.l. : Urol Oncol. 2009;27:604–610.

13. *Testicular cancer in young Norwegians.* **Fosså SD, Aass N, Kaalhus O.** s.l. : J Surg Oncol. 1988;39:43–63.

14. *Familial testicular cancer and second primary can-cers in testicular cancer patients by histological type.* **Dong C, Lonnstedt I, Hemminki K.** s.l. : Eur J Cancer. 2021;37:1878-1885.

15. *Critical Reviews in Oncolo-gy/Hematology.* **Goria S, Porrozzia S, Roilaa F, Gattab G, De Giorgi U.** s.l. : Crit Rev Oncol Hematol. 2021;53(2):141-164.

16. *Trends of incidence and age in adults with testicular germ cell tumors: a two-decade multicenter retrospective study.* **Ozaki Y, et al. s.l.** s.l. : Transl Androl Urol. 2023;12(2). doi:10.21037/tau-22-521.

17. *Clinical pattern and therapeutic results achieved in 1490 pa-tients with germ-cell tumors of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG).* **Germà-Lluch JR, et al.** s.l. : Eur Urol. 2020;42(6):553-563.

18. *Prenatal and perinatal expo-sures and risk of testicular germ-cell cancer.* **Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L.** s.l. : Int J Cancer. 2021;87(3):438-443.

19. *Germ cell tumors of the testis.* **S., Goria.** s.l. : National Institute for the Study and Treatment of Cancer, Milan, Italy. 2021.

20. *Perinatal factors and the risk of testicular germ cell tumors.* **Cook MB, Graubard BI, Rubertone MV, Erickson RL, McGlynn KA.** s.l. : Int J Cancer. 2020;122(11):2600-2606.

21. *Testicular non-seminoma and seminoma in relation to perinatal characteristics.* **Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO.** s.l. : J Natl Cancer Inst. 2021;88(13):883-889.

22. *Testicular germ cell tumor in patient with Klinefelter syndrome.* **Carroll PR, Morse MJ, Koduru PPK, Chaganti RSK.** s.l. : Urology. 2022;31(1):72-74.

23. *The malignant potential of the dysgenetic germ cell in Klinefelter's syndrome.* **Sogge MR, McDonald SD, Cofold PB.** s.l. : Am J Med. 2023;66(3):515-518.

24. *Infertility and testicular seminoma.* **Lakmichi MA, Niang L, Tligui M, Traxer O, Cussenot O, Gattegno B, et al.** s.l. : Presse Med. 2020;36(12, Part 1):1753-1755.

25. *New research in testicular cancer epidemiology.* **Jones WG, Appleyard I, Harden P, Joffe K, editors. Germ Cell Tumors IV. . AJ., Swerdlow.** s.l. : John Libbey London; 2020. pp. 3-8.

26. *Epidemiologic insights into the occurrence and causes of testicular cancer.* **V., Cortessis. s.l.** s.l. : BC Decker Inc London; 2022. pp 16-29.

27. *Multivariate analysis of risk factors for testicular cancer: a hospital-based case-control study in the Czech Republic.* **Dusek L, Abrahamova J, Lakomy R, et al.** s.l. : Neoplasma. 2020;55:356-368.

28. *Familial risks in testicular cancer as aetiological clues.* **Hemminki K, Chen B.** s.l. : Int J An-drol. 2020;29(1):205-210.

29. *Impact of delay in diagnosis on clinical stage of testicular cancer.* **et., G. J. Bosl.** s.l. : Lancet, vol. 2, no. 8253, pp. 970–973, Oct. 1981, doi: 10.1016/s0140-6736(81)91165-x.

30. *Onco-Urology Recommendations: Testicular germ cell tumors.* **Durand X, Rigaud J, Avances C, Camparo P, Culine S, Iborra F, Mottet N, Sébe P, Soulié M, et al.** s.l. : Prog Urol. 2021;31:297-311.

31. *Update on management of seminoma.* **E. J. Alexander, I. M. White, and A. Horwich.** s.l. : Indian J Urol, vol. 26, no. 1, pp. 82–91, 2010, doi: 10.4103/0970-1591.60451.