

Original Article

**Multidisciplinary Clinic Approach Improves Overall Survival Outcomes of Patients
with Metastatic Germ Cell Tumors**

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ABSTRACT

Background

To report our experience utilizing a multidisciplinary clinic (MDC) at Indiana University (IU) since the publication of the International Germ Cell Cancer Collaborative Group (IGCCCG), and to compare our overall survival to that of the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.

Patients and Methods

We conducted a retrospective analysis of all patients with metastatic germ cell tumor (GCT) seen at IU from 1998-2014. 1,611 consecutive patients were identified, of whom 704 patients received an initial evaluation by our MDC (including medical oncology, pathology, urology and thoracic surgery) and started first-line chemotherapy at IU.

These 704 patients were eligible for analysis. All patients in this cohort were treated with cisplatin-etoposide based combination chemotherapy. We compared the progression-free survival (PFS) and overall survival (OS) of patients treated at IU with that of the published IGCCCG cohort. OS of the IU testis cancer primary cohort (n=622) was further compared to the SEER data of 1283 patients labeled with "distant" disease. The Kaplan-Meier method was used to estimate progression-free survival and overall survival.

Results

With a median follow-up of 4.4 years, patients with good, intermediate, and poor risk disease by IGCCCG criteria treated at IU had 5-year PFS of 90%, 84%, and 54% and 5-year OS of 97%, 92%, and 73% respectively. The 5-year PFS for all patients in the IU

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3 cohort was 79% (95%CI, 76% to 82%). The 5-year OS for the IU cohort was 90% (95%
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5 CI, 87% to 92%). IU testis cohort had 5-year OS 94% (95% CI, 91% to 96%) vs. 75%
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7 (95% CI, 73% to 78%) for the SEER “distant” cohort between 2000-2014, P-value
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9 <0.0001.
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12 13 Conclusion

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16 The MDC approach to GCT at high-volume cancer center associated with improved
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18 overall survival outcomes in this contemporary dataset. OS is significantly higher in the
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20 IU cohort compared to the IGCCCG and SEER “distant” cohort.
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26 **Keywords:** Testicular cancer; Germ cell tumor; IGCCCG; Multidisciplinary, SEER
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30 31 Key message

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34 Herein, we investigated the role of multidisciplinary clinic approach in improving the
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36 outcomes of patients with metastatic germ cell tumors at our high volume cancer center
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38 at Indiana University (IU) and observed a better survival compared to the historical
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40 IGCCCG and the SEER distant cohort.
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INTRODUCTION

Germ-cell tumors (GCT) are the most common cancer in men between 15 and 35 years of age, with an estimated 8,720 cases diagnosed annually in the United States and 410 deaths [1]. First-line chemotherapy with bleomycin-etoposide-cisplatin (BEP) became the standard of care for patients with advanced GCT [2-5]. The International Germ-Cell Cancer Collaborative Group (IGCCCG) in 1997 published a consensus statement classifying patients with metastatic GCT into good, intermediate, and poor risk disease [6]. Good risk GCT had a 5-year progression-free survival (PFS) of 88% and a 5-year overall survival (OS) of 91%. Intermediate risk GCT had a 5-year PFS of 75% and a 5-year OS of 79%. The poor risk category had a 5-year PFS of 41% and a 5-year OS of 48%.

The optimal management of germ cell tumors is complex, with options including chemotherapy and surgery. At Indiana University Cancer Center (IU), we have established a multidisciplinary clinic (MDC) to evaluate newly diagnosed GCT patients and those needing additional consultation. The goals of this MDC are to provide state-of-the-art oncology care and to educate patients, their families, medical students, residents, and fellows in training. Our MDC integrate dedicated team including medical oncologists, pathologists, urologic and thoracic surgical oncologists, full-time coordinator (responsible for data acquisition, scheduling, and following up with patients and referring physicians) and oncology nurses. The team meets on a weekly basis in a multidisciplinary tumor board. Through this clinic, we can establish the accurate pathological diagnosis, offer combination chemotherapy, surgical resection of residual tumor and enroll patients on clinical trials all in one visit (Figure S2).

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3 Institutional experience, hospital and physician volume have been associated with
4 improved outcomes of testicular cancer [7-10]. Recent outcome data from large
5 datasets are missing, and the difference in results of patients treated in large volume
6 centers and community centers is unknown. We, therefore, report survival outcomes in
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8 704 consecutive patients with metastatic GCT treated at our MDC at IU since the
9 publication of IGCCCG and compare the outcome to those of National Cancer Institute
10 (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.
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20 **PATIENTS AND METHODS**

21 **Patients**

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24 The IU Cancer Registry database was queried, and a retrospective review was
25 performed to compare the PFS and OS of patients treated at IU with that of IGCCCG
26 [6]. This study used the secure Web-based, Title 21 Code of Federal Regulations Part
27 11-compliant Research Electronic Data Capture (REDCap) system for data input.
28 Eligible patients who had metastatic GCT treated at IU after the establishment of
29 IGCCCG between January 1998 and December 2014 were included. All patients were
30 treated with standard cisplatin-etoposide based combination chemotherapy consisting
31 of at least 3-4 cycles of cisplatin and etoposide with or without bleomycin or ifosfamide
32 [11, 12]. SEER Research Data (1973-2014) was also obtained to compare OS of the IU
33 cohort the SEER distant cohort. The SEER distant cohort consisted of patients in the
34 SEER database with testis cancer diagnosed between 2000-2014, who had a SEER
35 historical stage of distant, and who had available survival data [13].
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55 **Statistical Analysis**

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3 The endpoints of the study were the PFS and OS probabilities at 5 years. For the IU
4 cohort, PFS started with the initiation of chemotherapy and ended with progression or
5 death, whichever occurred first. OS started with the initiation of chemotherapy and
6 ended with the death of a patient. Survival status was identified from medical charts or
7 death certificates. Patients without an event were censored at the date of last follow-up.
8 For the SEER distant cohort, OS started with the date of diagnosis and ended with the
9 death of a patient. Patients alive at the date of last contact were censored. PFS and OS
10 were calculated according to the Kaplan-Meier method and using the log-rank test.
11 Analyses were completed compared using SAS software, version 9.4 and figures were
12 created in R, version 3.3.2. Five-year PFS and OS were reported along with 95%
13 confidence intervals calculated using the log-log method.
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30 RESULTS

31 Patient and Disease Characteristics

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33 For the IU cohort, 1611 consecutive patients with metastatic GCT were evaluated in the
34 MDC at IU between 1998 and 2014. Of these, 704 patients started the initial
35 chemotherapy at IU and were included in the primary outcome analysis (Figure S1).
36 Median age at diagnosis was 29 (range 13-62). Median follow-up time was 4.4 years.
37 The primary tumor site was testis in 622 (88.4%), retroperitoneum in 26 (3.7%), and
38 mediastinum in 54 (7.7%). 85% had non-seminomatous GCT (NSGCT). 97% of patients
39 were white, 1% were black, and the remaining 2% were a variety of races/ethnicities. Of
40 note, we did not include LDH in our database. Elevations in LDH are highly nonspecific
41 and may be found in a vast number of benign and malignant conditions [14]. Table 1
42 lists patients and disease characteristics at the time of initiation of first-line
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3 chemotherapy. Figure S3 presents a map of the United States showing the zip codes of
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5 patients seen at our center.
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9 For the SEER distant cohort, 1283 patients were identified from the SEER database
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11 with testis cancer diagnosed between 2000-2014. To be included in the cohort, patients
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13 must have had a SEER historical stage of distant and available survival data. Patients
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15 with a survival time of 0 (i.e., date of diagnosis and date of last contact are the same)
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17 were excluded. Median age at diagnosis was 32 (range 0-87). 87% of patients were
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19 white, 5% were black, and the remaining 8% were a variety of races/ethnicities. 73.5%
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21 had NSGCT.
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24 25 26 **Treatment Administration** 27

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29 All 704 evaluable patients in the IU cohort were treated with cisplatin-etoposide
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31 combination chemotherapy. Details regarding first-line treatment regimen stratified per
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33 IGCCCG risk classification are listed in Table 1. Overall, 82% of patients achieved a
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35 complete response (CR) and remained disease-free after first-line chemotherapy. A
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37 total of 250 patients (36%) underwent post-chemotherapy retroperitoneal lymph node
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39 dissection (PCRPLND), 129 (18%) thoracic surgery, 21 cervical lymph node dissection
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41 and nine patients had a resection of brain metastasis. 153 patients failed first-line
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43 chemotherapy, 118 received salvage chemotherapy including high dose chemotherapy
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45 (HDCT) ($n=76$), and 51 had salvage surgery. At last follow-up, 635 patients (90%) had
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47 no evidence of disease (NED), 65 patients (9%) had died, and four patients (1%) were
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49 alive with relapsed disease. Among patients who died, 52 patients were dead of disease
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51 progression, and 13 patients died of other causes including treatment-related toxicity,
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53 secondary malignancy or surgical complications.
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3 We also reviewed the GCT patients who came to IU for a second opinion. 907 patients
4 sought a second opinion or were evaluated after receiving first-line therapy at an
5 outside institution and were not included in the primary analysis. 492 (56%) underwent
6 PCRPLND, 432 (51%) underwent salvage chemotherapy, and 172 (21%) underwent
7 thoracic surgery as a result of the multidisciplinary evaluation.
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15 **Survival Outcomes**

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18 With a median follow-up of 4.4 years, the estimated 5-year PFS was 79% (95%CI, 76%
19 to 82%) and the 5-year OS was 90% (95% CI, 87% to 92%) for the IU cohort (Table 2).
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21 The 5-year PFS for good, Intermediate and poor risk were 90%, 84%, and 54%
22 respectively (Figure 1A) and the estimated 5-year OS was 97%, 92%, and 73% (Figure
23 1B), respectively. In sub-segment of patients with testis as the primary site at
24 presentation (IU testis cohort $n=622$), the 5-year OS was 94% (95% CI, 91% to 96%).
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26 Patients with primary mediastinal non-seminomatous GCT (PMNSGCT) had an
27 estimated 5-year PFS of 50% (95% CI, 35% to 63%) and 5-year OS of 59% (43% to
28 72%). Patients with brain metastasis at diagnosis had an estimated 5-year PFS of 15%
29 (5% to 28%) and 5-year OS of 46% (28% to 63%).
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43 To demonstrate the impact of our MDC approach, we compared OS of patients in the IU
44 testicular primary cohort with the SEER distant cohort. The 5-Year OS for the SEER
45 distant cohort was 75% (95% CI, 73% to 78%) compared to 94% (95% CI, 91% to 96%)
46 for IU testis cohort (P -value <0.0001 ; Figure 2). The SEER database does not allow
47 stratification according to IGCCCG risk category; therefore comparisons of survival
48 between groups are not possible.
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DISCUSSION

To our knowledge, this is the largest single-institution study evaluating survival outcomes of patients with metastatic GCT. Survival results of patients treated at IU appear superior to the results of the IGCCCG (Table 2) and the NCI SEER distant cohort (Figure 2). This observation is supported by a large multi-institutional initiative that provided outcome results from high-volume centers that were superior to the original IGCCCG [15]. These data were, however, not directly compared to community outcomes. Several factors may account for excellent survival outcomes seen at our center compared to the IGCCCG and SEER database. This could be attributed to the uniform utilization of cisplatin-etoposide based combination chemotherapy, improvement in supportive care avoiding delays between cycles, expertise in post-chemotherapy surgical resection of residual disease and the experience resulting from a large volume of patients. Our dedicated multidisciplinary team of medical, urologic and thoracic oncologists and pathologists have specific academic interest in GCT supported by strong research and clinical trials designed to refine treatment, improve supportive care, and patient education.

Surgical treatment is crucial for the management of metastatic GCT to improve survival and reduce complications [16, 17]. Appropriate patient selection and timing of surgery have lowered morbidity while improving oncologic outcomes at high volume centers [18, 19]. The marked improvement in OS in all-risk categories maybe driven by the development of successful salvage therapy options including salvage surgery, and the long-term experience in HDCT followed by autologous peripheral blood stem cell transplant (PBSCT) [20-25].

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3 This analysis has limitations. This is a retrospective single institution study, and
4 potential bias exists in our patient population. We didn't have access to matched
5 patient's characteristics between the contemporary IU cohort and the historical IGCCCG
6 cohort, and the community patients reported in SEER. Referral bias might have affected
7 the results of this study. However, this study has a large sample size of consecutive
8 patients with metastatic GCT treated at a tertiary care center with long follow-up. A large
9 portion of patients enrolled in the study had poor risk disease 25.7% compared to 14%
10 of patients from the IGCCCG [6]; hence survival outcomes for patients treated at other
11 institutions or in the community might vary. Besides, a limitation of this study is that NCI
12 SEER uses a staging system including local, regional and distant metastases which are
13 not typically used in germ cell tumor. The IGCCCG classification of good, intermediate
14 and poor risk is not included in the SEER database which makes further analysis not
15 possible. That is why we compared all patients with metastatic disease as one group.
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34 Despite substantial improvement in outcomes of patients with metastatic GCT treated in
35 the modern era, many challenges remain. There is a clear disparity in health care
36 outcomes among patients with testis cancer [26-28]. This could be related to patient's
37 factors such as under insurance, poor socioeconomic status, ethnicity, and a language
38 barrier that delays diagnosis. Also, it could be attributed to the rare nature of this cancer
39 and lack of experience in the community to establish an accurate diagnosis and deliver
40 a treatment plan.
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51 In conclusion, in this modern cohort of newly diagnosed metastatic GCT, there was an
52 improvement in PFS and OS for good, intermediate, and poor-risk disease compared to
53 IGCCCG. Furthermore, we demonstrated that a multidisciplinary team care approach
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3 are associated with improved survival outcomes compared to SEER distant cohort.
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5 Taken together, these data support reconstructing health delivery models to enhance
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7 value and improve clinical outcomes [9, 19].
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21 **Disclosure:** The authors have declared no conflicts of interest.
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24 25 26 27 **REFERENCES**

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FIGURE LEGENDS

- **Figure. 1:** Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) according to IGCCCG risk stratification

- **Figure. 2:** Kaplan-Meier estimates of overall survival of patients with newly diagnosed metastatic testicular GCT at the IU (1998-2014) and patients in NCI SEER (2000-2014).

Online Only

- **Figure. S1:** Study flow chart of 704 patients with metastatic germ-cell tumor treated at Indiana University between 1998 and 2014

- **Figure S2:** Diagram of the patients flow through the multidisciplinary GCT clinic.

- **Figure S3:** Map of the United States based on the zip codes of patients seen at our MDC.

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ABSTRACT

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26 **Keywords:** Testicular cancer; Germ cell tumor; IGCCCG; Multidisciplinary, SEER
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34 Herein, we investigated the role of multidisciplinary clinic approach in improving the
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36 outcomes of patients with metastatic germ cell tumors at our high volume cancer center
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38 at Indiana University (IU) and observed a better survival compared to the historical
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40 IGCCCG and the SEER distant cohort.
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INTRODUCTION

Germ-cell tumors (GCT) are the most common cancer in men between 15 and 35 years of age, with an estimated 8,720 cases diagnosed annually in the United States and 410 deaths [1]. First-line chemotherapy with bleomycin-etoposide-cisplatin (BEP) became the standard of care for patients with advanced GCT [2-5]. The International Germ-Cell Cancer Collaborative Group (IGCCCG) in 1997 published a consensus statement classifying patients with metastatic GCT into good, intermediate, and poor risk disease [6]. Good risk GCT had a 5-year progression-free survival (PFS) of 88% and a 5-year overall survival (OS) of 91%. Intermediate risk GCT had a 5-year PFS of 75% and a 5-year OS of 79%. The poor risk category had a 5-year PFS of 41% and a 5-year OS of 48%.

The optimal management of germ cell tumors is complex, with options including chemotherapy and surgery. At Indiana University Cancer Center (IU), we have established a multidisciplinary clinic (MDC) to evaluate newly diagnosed GCT patients and those needing additional consultation. The goals of this MDC are to provide state-of-the-art oncology care and to educate patients, their families, medical students, residents, and fellows in training. Our MDC integrate dedicated team including medical oncologists, pathologists, urologic and thoracic surgical oncologists, full-time coordinator (responsible for data acquisition, scheduling, and following up with patients and referring physicians) and oncology nurses. The team meets on a weekly basis in a multidisciplinary tumor board. Through this clinic, we can establish the accurate pathological diagnosis, offer combination chemotherapy, surgical resection of residual tumor and enroll patients on clinical trials all in one visit (Figure S2).

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3 Institutional experience, hospital and physician volume have been associated with
4 improved outcomes of testicular cancer [7-10]. Recent outcome data from large
5 datasets are missing, and the difference in results of patients treated in large volume
6 centers and community centers is unknown. We, therefore, report survival outcomes in
7 704 consecutive patients with metastatic GCT treated at our MDC at IU since the
8 publication of IGCCCG and compare the outcome to those of National Cancer Institute
9 (NCI) Surveillance, Epidemiology, and End Results (SEER) Program.
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20 **PATIENTS AND METHODS**

21 **Patients**

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24 The IU Cancer Registry database was queried, and a retrospective review was
25 performed to compare the PFS and OS of patients treated at IU with that of IGCCCG
26 [6]. This study used the secure Web-based, Title 21 Code of Federal Regulations Part
27 11-compliant Research Electronic Data Capture (REDCap) system for data input.
28 Eligible patients who had metastatic GCT treated at IU after the establishment of
29 IGCCCG between January 1998 and December 2014 were included. All patients were
30 treated with standard cisplatin-etoposide based combination chemotherapy consisting
31 of at least 3-4 cycles of cisplatin and etoposide with or without bleomycin or ifosfamide
32 [11, 12]. SEER Research Data (1973-2014) was also obtained to compare OS of the IU
33 cohort the SEER distant cohort. The SEER distant cohort consisted of patients in the
34 SEER database with testis cancer diagnosed between 2000-2014, who had a SEER
35 historical stage of distant, and who had available survival data [13].
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55 **Statistical Analysis**

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3 The endpoints of the study were the PFS and OS probabilities at 5 years. For the IU
4 cohort, PFS started with the initiation of chemotherapy and ended with progression or
5 death, whichever occurred first. OS started with the initiation of chemotherapy and
6 ended with the death of a patient. Survival status was identified from medical charts or
7 death certificates. Patients without an event were censored at the date of last follow-up.
8 For the SEER distant cohort, OS started with the date of diagnosis and ended with the
9 death of a patient. Patients alive at the date of last contact were censored. PFS and OS
10 were calculated according to the Kaplan-Meier method and using the log-rank test.
11 Analyses were completed compared using SAS software, version 9.4 and figures were
12 created in R, version 3.3.2. Five-year PFS and OS were reported along with 95%
13 confidence intervals calculated using the log-log method.
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30 RESULTS

31 Patient and Disease Characteristics

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33 For the IU cohort, 1611 consecutive patients with metastatic GCT were evaluated in the
34 MDC at IU between 1998 and 2014. Of these, 704 patients started the initial
35 chemotherapy at IU and were included in the primary outcome analysis (Figure S1).
36 Median age at diagnosis was 29 (range 13-62). Median follow-up time was 4.4 years.
37 The primary tumor site was testis in 622 (88.4%), retroperitoneum in 26 (3.7%), and
38 mediastinum in 54 (7.7%). 85% had non-seminomatous GCT (NSGCT). 97% of patients
39 were white, 1% were black, and the remaining 2% were a variety of races/ethnicities. Of
40 note, we did not include LDH in our database. Elevations in LDH are highly nonspecific
41 and may be found in a vast number of benign and malignant conditions [14]. Table 1
42 lists patients and disease characteristics at the time of initiation of first-line
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3 chemotherapy. Figure S3 presents a map of the United States showing the zip codes of
4 patients seen at our center.
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9 For the SEER distant cohort, 1283 patients were identified from the SEER database
10 with testis cancer diagnosed between 2000-2014. To be included in the cohort, patients
11 must have had a SEER historical stage of distant and available survival data. Patients
12 with a survival time of 0 (i.e., date of diagnosis and date of last contact are the same)
13 were excluded. Median age at diagnosis was 32 (range 0-87). 87% of patients were
14 white, 5% were black, and the remaining 8% were a variety of races/ethnicities. 73.5%
15 had NSGCT.
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24 **Treatment Administration**

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26 All 704 evaluable patients in the IU cohort were treated with cisplatin-etoposide
27 combination chemotherapy. Details regarding first-line treatment regimen stratified per
28 IGCCCG risk classification are listed in Table 1. Overall, 82% of patients achieved a
29 complete response (CR) and remained disease-free after first-line chemotherapy. A
30 total of 250 patients (36%) underwent post-chemotherapy retroperitoneal lymph node
31 dissection (PCRPLND), 129 (18%) thoracic surgery, 21 cervical lymph node dissection
32 and nine patients had a resection of brain metastasis. 153 patients failed first-line
33 chemotherapy, 118 received salvage chemotherapy including high dose chemotherapy
34 (HDCT) ($n=76$), and 51 had salvage surgery. At last follow-up, 635 patients (90%) had
35 no evidence of disease (NED), 65 patients (9%) had died, and four patients (1%) were
36 alive with relapsed disease. Among patients who died, 52 patients were dead of disease
37 progression, and 13 patients died of other causes including treatment-related toxicity,
38 secondary malignancy or surgical complications.
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3 We also reviewed the GCT patients who came to IU for a second opinion. 907 patients
4 sought a second opinion or were evaluated after receiving first-line therapy at an
5 outside institution and were not included in the primary analysis. 492 (56%) underwent
6 PCRPLND, 432 (51%) underwent salvage chemotherapy, and 172 (21%) underwent
7 thoracic surgery as a result of the multidisciplinary evaluation.
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15 **Survival Outcomes**

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18 With a median follow-up of 4.4 years, the estimated 5-year PFS was 79% (95%CI, 76%
19 to 82%) and the 5-year OS was 90% (95% CI, 87% to 92%) for the IU cohort (Table 2).
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21 The 5-year PFS for good, Intermediate and poor risk were 90%, 84%, and 54%
22 respectively (Figure 1A) and the estimated 5-year OS was 97%, 92%, and 73% (Figure
23 1B), respectively. In sub-segment of patients with testis as the primary site at
24 presentation (IU testis cohort $n=622$), the 5-year OS was 94% (95% CI, 91% to 96%).
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26 Patients with primary mediastinal non-seminomatous GCT (PMNSGCT) had an
27 estimated 5-year PFS of 50% (95% CI, 35% to 63%) and 5-year OS of 59% (43% to
28 72%). Patients with brain metastasis at diagnosis had an estimated 5-year PFS of 15%
29 (5% to 28%) and 5-year OS of 46% (28% to 63%).
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43 To demonstrate the impact of our MDC approach, we compared OS of patients in the IU
44 testicular primary cohort with the SEER distant cohort. The 5-Year OS for the SEER
45 distant cohort was 75% (95% CI, 73% to 78%) compared to 94% (95% CI, 91% to 96%)
46 for IU testis cohort (P -value <0.0001 ; Figure 2). The SEER database does not allow
47 stratification according to IGCCCG risk category; therefore comparisons of survival
48 between groups are not possible.
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DISCUSSION

To our knowledge, this is the largest single-institution study evaluating survival outcomes of patients with metastatic GCT. Survival results of patients treated at IU appear superior to the results of the IGCCCG (Table 2) and the NCI SEER distant cohort (Figure 2). This observation is supported by a large multi-institutional initiative that provided outcome results from high-volume centers that were superior to the original IGCCCG [15]. These data were, however, not directly compared to community outcomes. Several factors may account for excellent survival outcomes seen at our center compared to the IGCCCG and SEER database. This could be attributed to the uniform utilization of cisplatin-etoposide based combination chemotherapy, improvement in supportive care avoiding delays between cycles, expertise in post-chemotherapy surgical resection of residual disease and the experience resulting from a large volume of patients. Our dedicated multidisciplinary team of medical, urologic and thoracic oncologists and pathologists have specific academic interest in GCT supported by strong research and clinical trials designed to refine treatment, improve supportive care, and patient education.

Surgical treatment is crucial for the management of metastatic GCT to improve survival and reduce complications [16, 17]. Appropriate patient selection and timing of surgery have lowered morbidity while improving oncologic outcomes at high volume centers [18, 19]. The marked improvement in OS in all-risk categories maybe driven by the development of successful salvage therapy options including salvage surgery, and the long-term experience in HDCT followed by autologous peripheral blood stem cell transplant (PBSCT) [20-25].

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3 This analysis has limitations. This is a retrospective single institution study, and
4 potential bias exists in our patient population. We didn't have access to matched
5 patient's characteristics between the contemporary IU cohort and the historical IGCCCG
6 cohort, and the community patients reported in SEER. Referral bias might have affected
7 the results of this study. However, this study has a large sample size of consecutive
8 patients with metastatic GCT treated at a tertiary care center with long follow-up. A large
9 portion of patients enrolled in the study had poor risk disease 25.7% compared to 14%
10 of patients from the IGCCCG [6]; hence survival outcomes for patients treated at other
11 institutions or in the community might vary. Besides, a limitation of this study is that NCI
12 SEER uses a staging system including local, regional and distant metastases which are
13 not typically used in germ cell tumor. The IGCCCG classification of good, intermediate
14 and poor risk is not included in the SEER database which makes further analysis not
15 possible. That is why we compared all patients with metastatic disease as one group.
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34 Despite substantial improvement in outcomes of patients with metastatic GCT treated in
35 the modern era, many challenges remain. There is a clear disparity in health care
36 outcomes among patients with testis cancer [26-28]. This could be related to patient's
37 factors such as under insurance, poor socioeconomic status, ethnicity, and a language
38 barrier that delays diagnosis. Also, it could be attributed to the rare nature of this cancer
39 and lack of experience in the community to establish an accurate diagnosis and deliver
40 a treatment plan.
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51 In conclusion, in this modern cohort of newly diagnosed metastatic GCT, there was an
52 improvement in PFS and OS for good, intermediate, and poor-risk disease compared to
53 IGCCCG. Furthermore, we demonstrated that a multidisciplinary team care approach
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are associated with improved survival outcomes compared to SEER distant cohort.

Taken together, these data support reconstructing health delivery models to enhance value and improve clinical outcomes [9, 19].

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22 **FIGURE LEGENDS**

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25 - **Figure. 1:** Kaplan-Meier estimates of progression-free survival (A) and overall survival
26 (B) according to IGCCCG risk stratification
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29 - **Figure. 2:** Kaplan-Meier estimates of overall survival of patients with newly diagnosed
30 metastatic testicular GCT at the IU (1998-2014) and patients in NCI SEER (2000-2014).
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37 - **Figure. S1:** Study flow chart of 704 patients with metastatic germ-cell tumor treated at
38 Indiana University between 1998 and 2014
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41 - **Figure S2:** Diagram of the patients flow through the multidisciplinary GCT clinic.
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45 - **Figure S3:** Map of the United States based on the zip codes of patients seen at our
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Figure 1 (A)

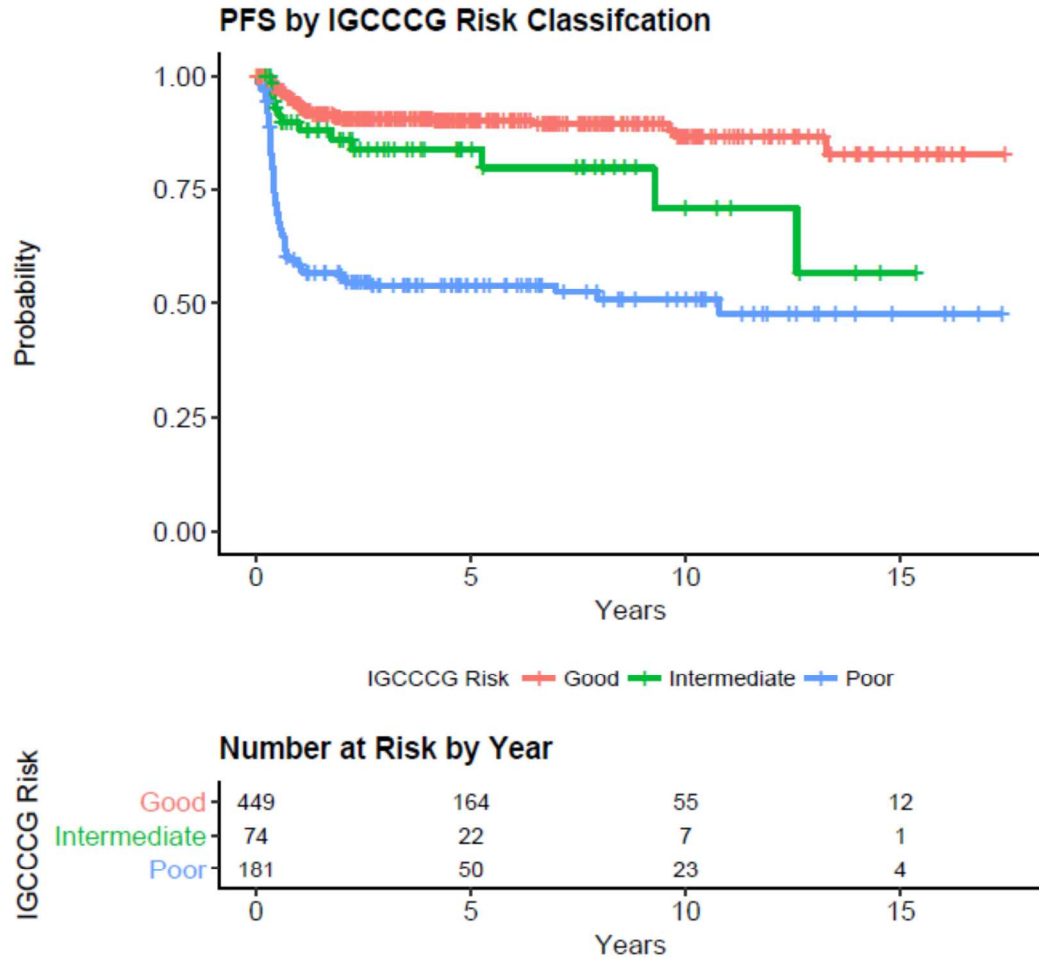
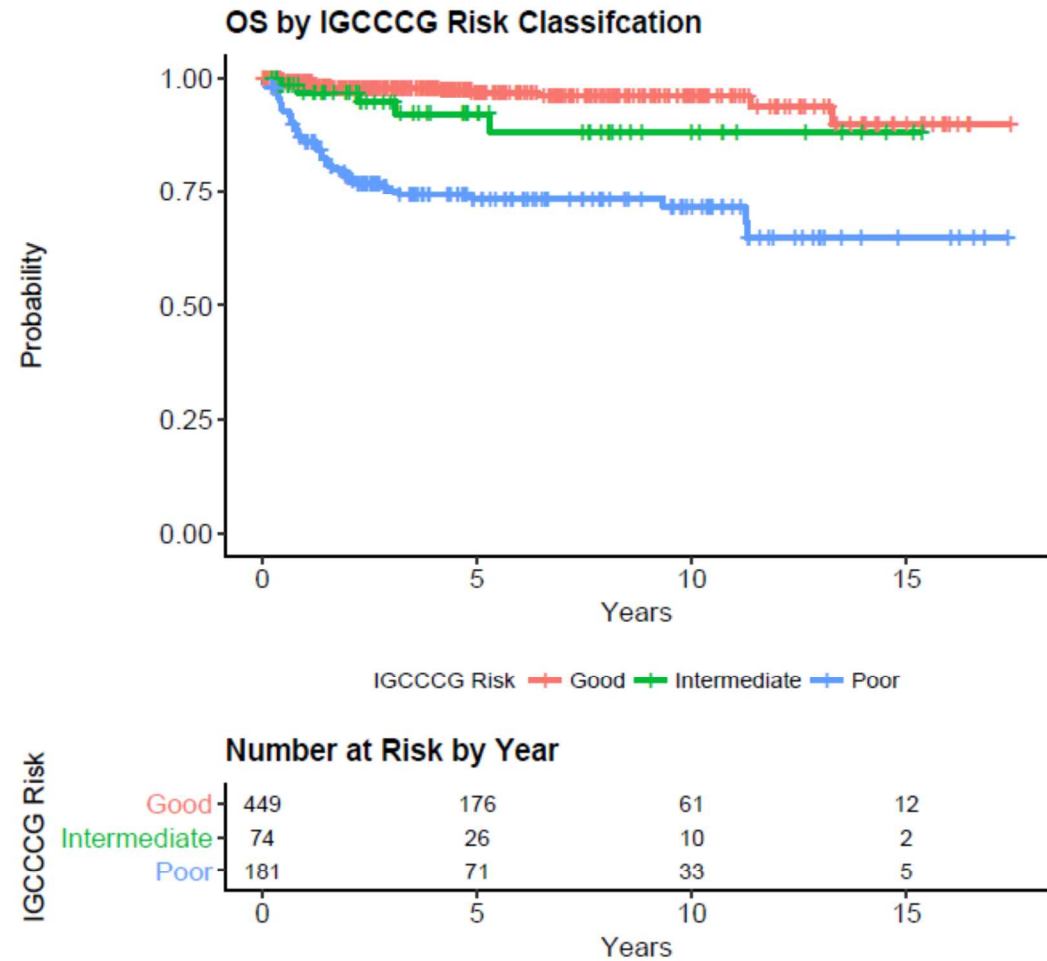


Figure. 1 (B)

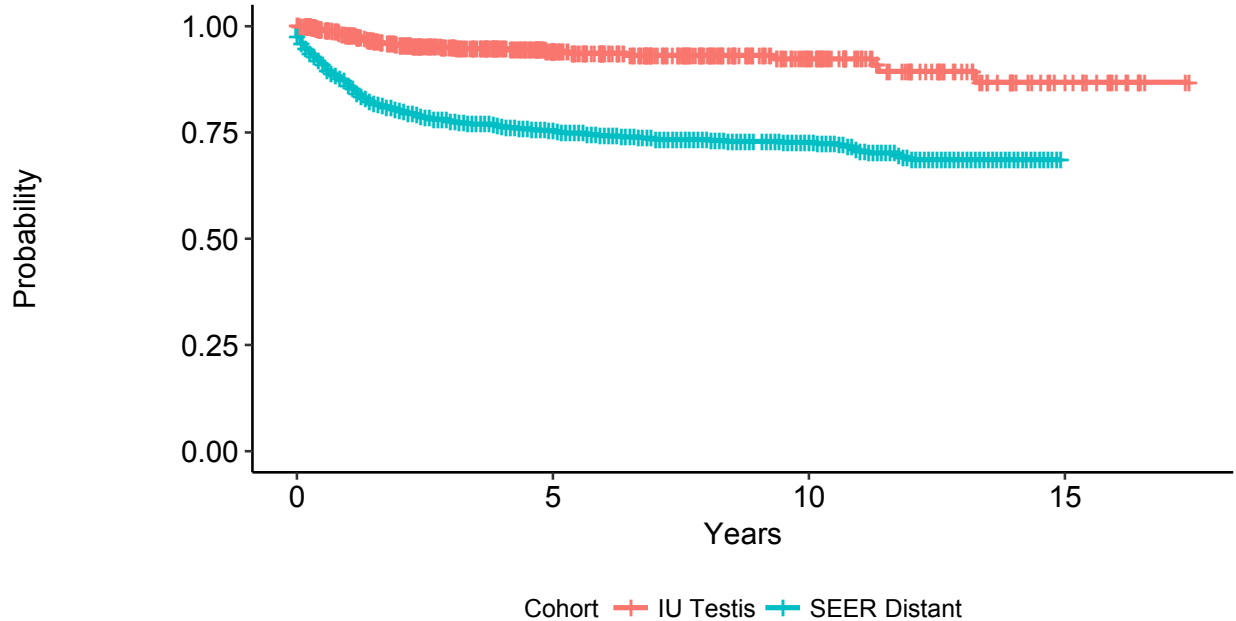


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Figure 2

Comparing OS between the IU Testis and SEER Distant Cohorts



Number at Risk by Year

Cohort	0	5	10	15
IU Testis	622	247	92	17
SEER Distant	1283	566	252	0

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Table 1. Patient and disease characteristics at the beginning of first-line chemotherapy

CHARACTERISTIC	OVERALL (N=704)	GOOD ⁺ (N=449; 63.8%)	INTERMEDIATE ⁺ (N=74; 10.5%)	POOR ⁺ (N=181; 25.7%)
MEDIAN AGE (RANGE)	29.3 (13.1-61.5)	30.54 (14.9- 61.5)	26.8 (16.0-49.6)	26.9 (13.1-55.7)
LOCATION OF PRIMARY TUMOR	622 (88.4%)	433 (96.4%)	70 (94.6%)	119 (65.8%)
• TESTIS	26 (3.7%)	9 (2.0%)	1 (1.4%)	14 (7.7%)
• RETROPERITONEUM	54 (7.7%)	5 (1.1%)	0	48 (26.5%)
• MEDIASTINUM	2 (0.2%)	2 (0.5%)		0
• UNKNOWN				
TUMOR HISTOLOGY	106 (15.1%)	99 (22.1%)	7 (9.5%)	0
• SEMINOMA	598 (84.9%)	350 (77.9%)	67 (90.5%)	181 (100%)
• NSGCT				
PREDOMINANT HISTOLOGY				
• EMBRYONAL	257 (36.5%)	205 (45.7%)	22 (29.7%)	30 (16.6%)
• CHORIOCARCINOMA	48 (6.8%)	1 (0.2%)	9 (12.2%)	44 (24.3%)
• YOLK SAC TUMOR	69 (9.8%)	16 (3.6%)	7 (9.5%)	29 (16.0%)
• TERATOMA	65 (9.2%)	29 (6.5%)	21 (28.4%)	30 (16.6%)
• MIXED	104 (14.8%)	53 (11.8%)	3 (4.0%)	1 (0.6%)
• SEMINOMA	63 (9.0%)	79 (11.2%)	5 (6.8%)	0
• PURE SEMINOMA	79 (11.2%)	11 (1.6%)	2 (2.7%)	4 (2.2%)
• NECROSIS	11 (1.6%)	59 (13.1%)	0	1 (0.6%)
• IGCN (CIS)	8 (1.1%)	74 (16.5%)		
		5 (1.1%)		
		7 (1.6%)		
MEDIAN SERUM AFP NG/ML (RANGE)	10.8 (0.2-280000)	5.9 (0.2-999)	1323.6 (0.6-9653)	270.3 (0.9- 280000)
SERUM AFP				
• < 1,000	578 (82.8%)	444 (100%)	29 (39.2%)	105 (58.3%)
• 1,000-10,000	79 (11.3%)	0	45 (60.8%)	34 (18.9%)
• ≥ 10,000	41 (5.9%)	0	0	41 (22.8%)
MEDIAN SERUM HCG MIU/ML (RANGE)	21.7 (0-1700000)	6.2 (0-4981.9)	1334.5 (0-41000)	10838.0 (0.5- 1700000)
SERUM HCG				
• < 5,000	571 (81.8%)	444 (100%)	44 (59.5%)	83 (46.1%)
• 5,000-50,000	51 (7.3%)	0	30 (40.5%)	21 (11.7%)
• ≥ 50,000	76 (10.9%)	0	0	76 (42.2%)
		0		

METASTATIC SITE(S)				
• RETROPERITONEUM	555 (78.8%)	362	68 (91.9%)	125
• PULMONARY	270 (38.4%)	(80.6%)	41 (55.4%)	(69.1%)
• NPVM	93 (13.2%)	96	5 (6.8%)	133
-LIVER	60 (8.5%)	(21.4%)	1 (1.4%)	(73.5%)
-BRAIN *	34 (4.8%)	0	3 (4.1%)	88 (48.6%)
-BONE *	16 (2.3%)	0	2 (2.7%)	59 (32.6%)
-OTHER	12 (1.7%)	0	1 (1.4%)	31 (17.1%)
		0		14 (7.7%)
		0		11 (6.1%)
FIRST-LINE CHEMOTHERAPY				
• BEPX3	384 (54.6%)	371	7 (9.5%)	6 (3.3%)
• BEPX4	123 (17.5%)	(82.6%)	26 (35.1%)	91 (50.3%)
• BEPX3+EPX1	69 (9.8%)	6 (1.3%)	33 (44.6%)	21 (11.6%)
• EPX4	42 (6.0%)	15 (3.3%)	1 (1.3%)	0
• VIPX4	50 (7.1%)	41 (9.1%)	2 (2.7%)	48 (26.5%)
• OTHER	36 (5.1%)	0	5 (6.8%)	15 (8.3%)
		16 (3.6%)		

ABBREVIATIONS: NPVM, NON-PULMONARY VISCERAL METASTASIS; IGCCCG, INTERNATIONAL GERM CELL CANCER COLLABORATIVE GROUP; AFP, ALPHA FETOPROTEIN; HCG, HUMAN CHORIONIC GONADOTROPIN; IU, INTERNATIONAL UNIT; NSGCT, NON-SEMINOMATOUS GERM CELL TUMOR; IGCN, INTRATUBULAR GERM CELL NEOPLASIA

*BRAIN/BONE IMAGING WAS NOT MANDATORY

*RISK PER IGCCCG CLASSIFICATION

For Review

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Table 2. Comparison of Survival Outcomes between the IGCCCG, IU and NCI SEER Dataset

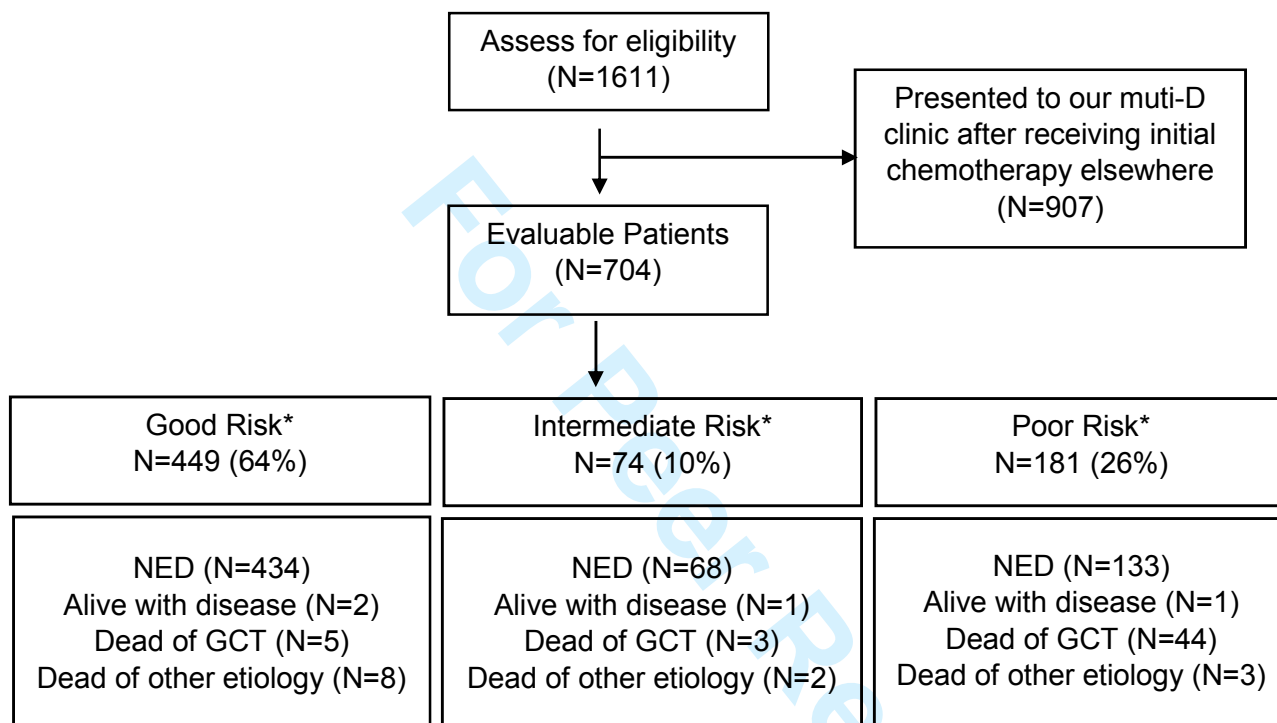
RISK PER IGCCCG CRITERIA	5-YEAR	INDIANA UNIVERSITY 1998-2014	IGCCCG 1975-1990	NCI SEER 2000-2013
GOOD RISK	PFS	90%	88%	NA
	OS	97%	91%	
INTERMEDIATE RISK	PFS	84%	75%	NA
	OS	92%	79%	
POOR RISK	PFS	54%	41%	NA
	OS	73%	48%	
TESTIS CANCER COHORT	OS	94%	NA	75%
Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group; PFS, progression-free survival; OS, overall survival, NCI SEER: National Cancer Institute Surveillance, Epidemiology, and End Results Program.				

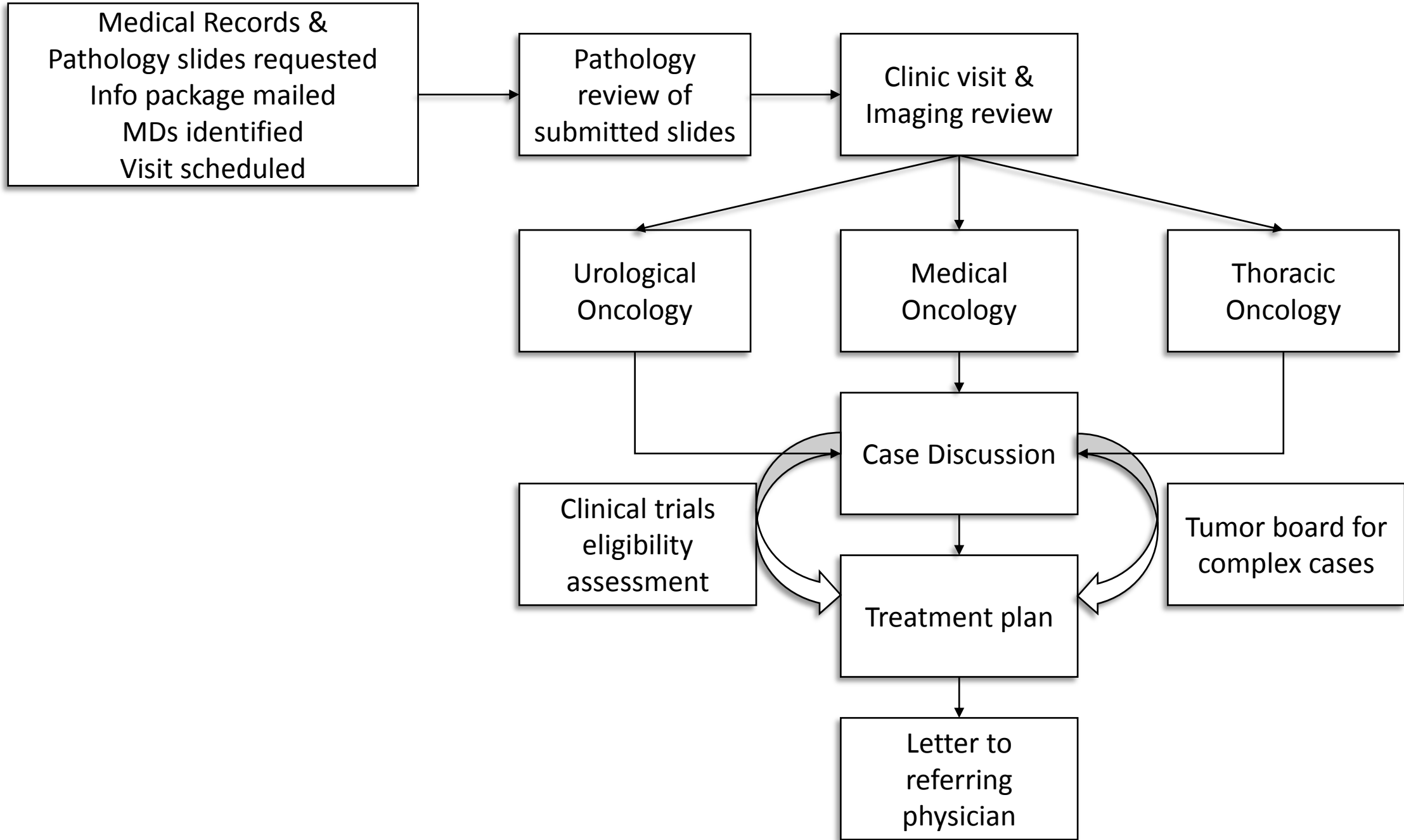
Peer Review

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Figure. S1

Abbreviations: *Risk is per International Germ Cell Cancer Collaborative Group criteria; NED, no evidence of disease; GCT, germ-cell tumor





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