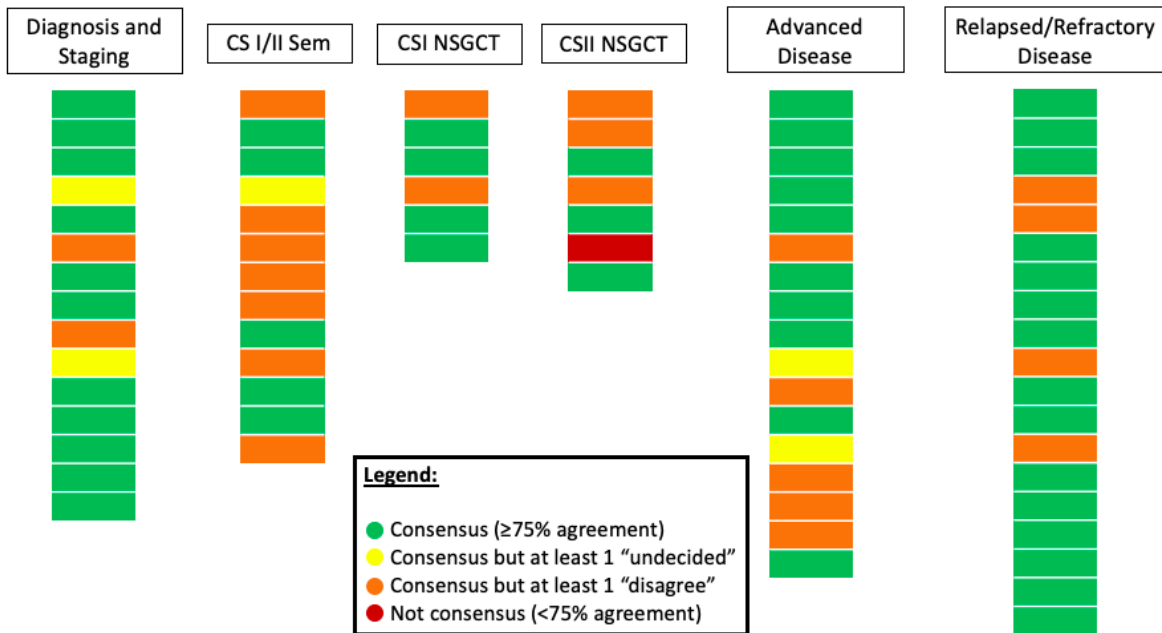
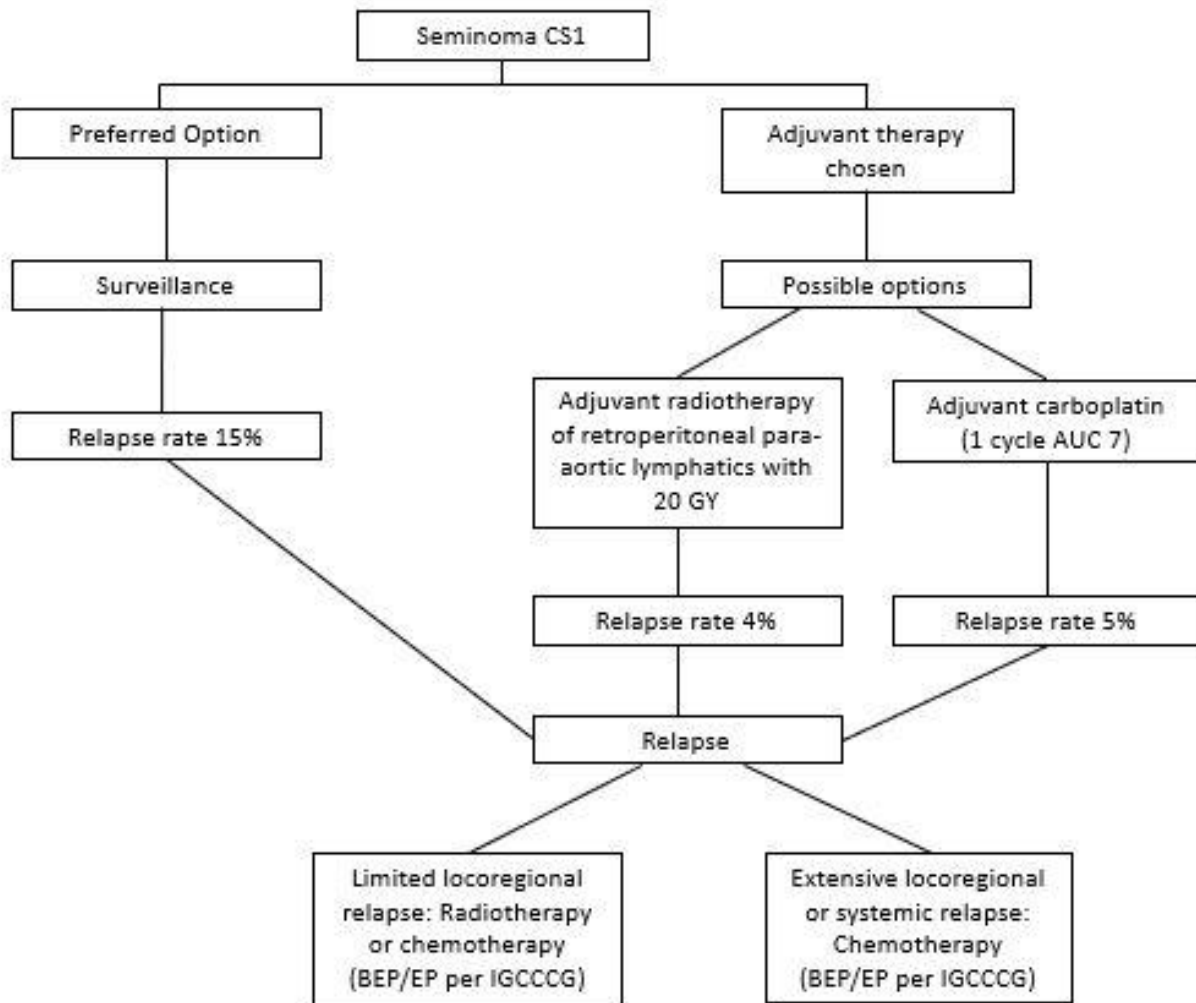


APPENDIX

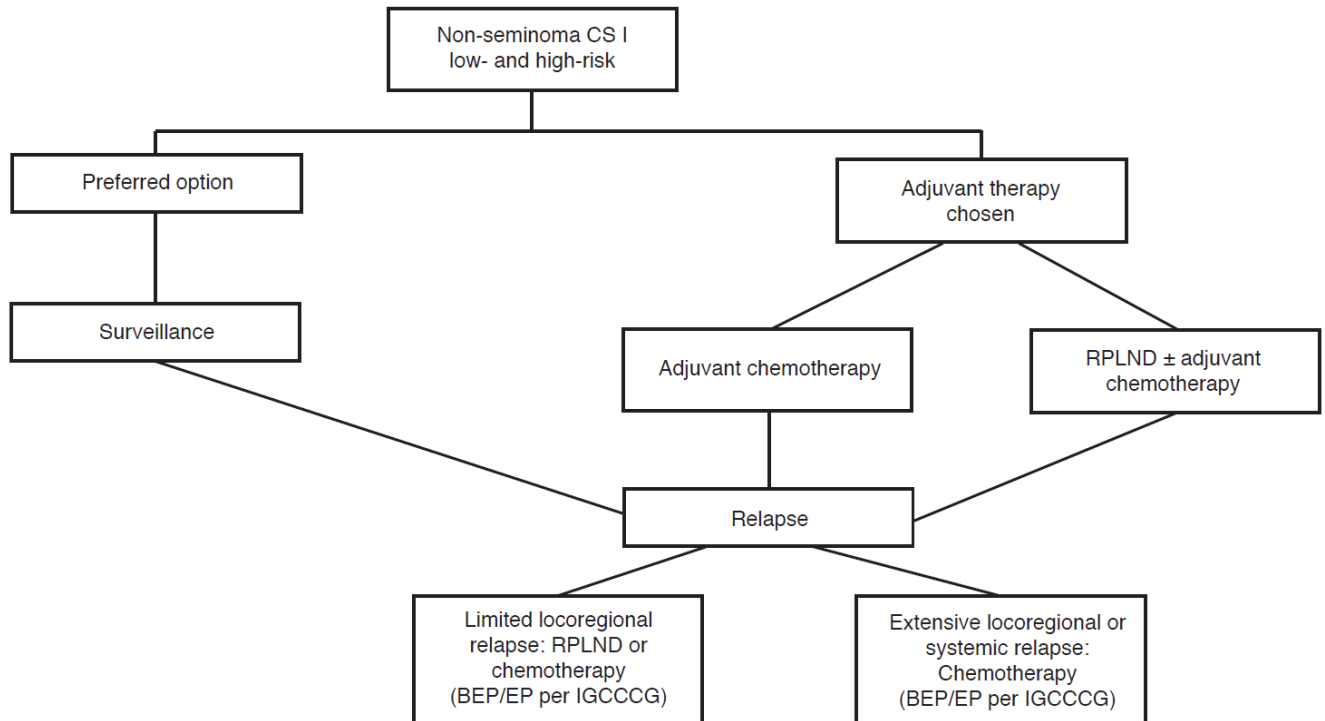
Supplementary Figure 1. Overview of initial survey results for each stage-specific topic.



Supplementary Figure 2. Schema for the management of stage I seminoma (CS1). BEP: bleomycin, etoposide, cisplatin; IGCCC: International Germ Cell Cancer Collaborative Group.



Supplementary Figure 3. Schema for the management of stage I non-seminoma (CS1). IGCCC: International Germ Cell Cancer Collaborative Group; RPLND: retroperitoneal lymph node dissection.



| Supplementary Table 1. Staging of testis tumors: UICC/American Joint Committee on Cancer (8th edition)¹ | | |
|---|-------------|--|
| TNM staging | Unit | Value |
| Primary tumor (pT) | pTX | Primary tumor cannot be assessed |
| | pT0 | No evidence of primary tumor |
| | pTis | Germ cell neoplasia in situ |
| | pT1 | Tumor limited to testis (including rete testis invasion) without lymphovascular invasion |
| | pT1a | Tumor smaller than 3 cm in size [#] |
| | pT1b | Tumor 3 cm or larger in size [#] |
| | pT2 | Tumor limited to the testis (including rete testis invasion) with lymphovascular invasion OR Tumor invading hilar soft tissue or epididymis or penetrating visceral |

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| | | | | |
|---|-----|--|-----|---|
| | | mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion | | |
| | pT3 | Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion | | |
| | pT4 | Tumor invades scrotum with or without lymphovascular invasion | | |
| Regional lymph nodes (pN and cN) | NX | Regional lymph node cannot be assessed | | |
| | pN0 | No regional lymph node metastasis | cN0 | No regional lymph node metastasis |
| | pN1 | Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension | cN1 | Metastasis with a lymph node mass ≤ 2 cm in greatest dimension OR multiple lymph nodes, none > 2 cm in greatest dimension |
| | pN2 | Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor | cN2 | Metastasis with a lymph node mass > 2 cm but ≤ 5 cm in greatest dimension OR multiple lymph nodes, any one mass > 2 cm but ≤ 5 cm in greatest dimension |
| | pN3 | Metastasis with a lymph node mass larger than 5 cm in greatest dimension | cN3 | Metastasis with a lymph node mass > 5 cm in greatest dimension |
| Distant metastasis (M) | M1 | Distant metastasis | | |
| | M1a | Non-retroperitoneal nodal or pulmonary metastases | | |
| | M1b | Non-pulmonary visceral metastases | | |
| Serum tumor markers (S) | SX | Serum marker studies not available or performed | | |
| | S0 | Marker study levels within normal limits | | |
| | S1 | LDH $< 1.5 \times$ normal and HCG (IU/L) < 5000 and AFP (ug/L) < 1000 | | |

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| | | | | |
|-----------------------|--------------|---|-------------------|---------------------|
| | S2 | LDH 1.5–10 × normal or HCG (IU/L) 5000–50 000 or AFP (ug/L) 1000–10 000 | | |
| | S3 | LDH >10 × normal or HCG (IU/L) >50 000 or AFP (ug/L) >10 000 | | |
| Stage grouping | | | | |
| Stage | Tumor | Node | Metastasis | Serum factor |
| 0 | pTis | N0 | M0 | S0 |
| I | pT1-4 | N0 | M0 | SX |
| IA | pT1 | N0 | M0 | S0 |
| IB | pT2 | N0 | M0 | S0 |
| | pT3 | | M0 | S0 |
| | pT4 | | M0 | S0 |
| IS | Any T | N0 | M0 | S1-3 |
| II | Any T | N1-3 | M0 | SX |
| IIA | Any T | N1 | M0 | S0 |
| | Any T | N1 | M0 | S1 |
| IIB | Any T | N2 | M0 | S0 |
| | Any T | N2 | M0 | S1 |
| IIC | Any T | N3 | M0 | S0 |
| | Any T | N3 | M0 | S1 |
| III | Any T | Any N | M1 | SX |
| IIIA | Any T | Any N | M1a | S0 |
| | Any T | Any N | M1a | S1 |
| IIIB | Any T | N1-3 | M0 | S2 |
| | Any T | Any N | M1a | S2 |
| IIIC | Any T | N1-3 | M0 | S3 |
| | Any T | Any N | M1a | S3 |
| | Any T | Any N | M1b | Any S |

#Subclassification of pT1 applies only to pure seminoma. AFP: alpha-fetoprotein; HCG: human chorionic gonadotrophin; LDH: lactate dehydrogenase.

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| Supplementary Table 2. Summary of surveillance studies in stage I seminoma | | | | | | |
|---|-------------|---------------------------------|---------------------|-----------------------------|------------------|----------------------------------|
| Author | Year | Median followup (months) | No. patients | No. patients relapse | Relapse % | Cause-specific survival % |
| Ramakrishnan ² | 1992 | 44 | 72 | 13 | 18 | 100 |
| Von der Maase ³ | 1993 | 48 | 261 | 49 | 18.8 | 98.9 |
| Warde ⁴ | 2005 | 98 | 421 | 64 | 15.2 | 99.7 |
| Tyldesley ⁵ | 2006 | 33 | 93 | 16 | 17.2 | 97.8 |
| Tandstad ⁶ | 2011 | 62 | 512 | 65 | 12.7 | 99.8 |
| Mortensen ⁷ | 2014 | 181 | 1954 | 369 | 18.9 | 99.3 |
| Aparicio ⁸ | 2014 | 80 | 744 | 63 | 11.1 | 100 |
| Chung ⁹ | 2014 | 46 | 685 | 88 | 12.8 | 99 |
| Kollmannsberge ¹⁰ | 2015 | 52 | 1344 | 173 | 13 | 99.9 |

| Supplementary Table 3. Adjuvant radiation therapy studies in stage I seminoma | | | | |
|--|-----------------------|---------------------|------------------|----------------------------------|
| Author | Years of study | No. patients | Relapse % | Cause-specific survival % |
| Fosså ¹¹ | 1989–1993 | 478 | 3.8 | 100 |
| Jones ¹² | 1995–1998 | 625 | 3.5 | 99.6 |
| Santoni ¹³ | 1970–1999 | 487 | 4.3 | 99.4 |
| Oliver ¹⁴ | 1996–2001 | 904 | 4.0 | 99.9 |
| Tandstad ⁶ | 2000–2006 | 481 | 0.8 | 99 |
| Soper ¹⁵ | 1990–2010 | 329 | 2.8 | 99.3 |
| Hosni ¹⁶ | 1981–2011 | 294 | 5.0 | 100 |

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| Supplementary Table 4. Summary of surveillance studies in stage I non-seminoma | | | | | | |
|---|-----------------------|---------------------|---------------------------------|-----------------------|---------------------|--------------|
| Author (publication year) Site | Years of study | No. patients | Median followup (months) | Relapses n (%) | Deaths n (%) | DSS % |
| Divrik (2006) ¹⁷ <i>Turkey</i> | 1993–2005 | 211 | 75 | 66 (31) | 5 (2) | 98 |
| Daugaard (2003) ¹⁸ <i>Denmark</i> | 1984–2001 | 301 | 60 | 86 (29) | 0 (0) | 99 |
| Roeleveld (2001) ¹⁹ <i>Netherlands</i> | 1982–1994 | 90 | 97 | 23 (26) | 1 (1) | 99 |
| Alexandre (2001) ²⁰ <i>France</i> | 1984–1996 | 88 | 52 | 24 (27) | 1 (1) | 98 |
| Francis (2000) ²¹ <i>United Kingdom</i> | 1979–1996 | 183 | 70 | 52 (28) | 2 (1) | 99 |
| Sogani (1998) ²² <i>Memorial Sloan-Kettering Cancer Center, NY</i> | 1979–1987 | 105 | 136 | 27 (26) | 3 (3) | 97 |
| Colls (1999) ²³ <i>New Zealand</i> | 1980–1997 | 248 | 53 | 70 (28) | 4 (2) | 98 |
| Hao (1998) ²⁴ <i>Tom Baker Cancer Centre, Calgary</i> | 1980–1994 | 76 | 49 | 28 (37) | 2 (3) | 97 |
| Boyer (1997) ²⁵ <i>Australia</i> | 1982–1995 | 77 | 58 | 27 (35) | 2 (3) | 97 |
| Nicolai (1995) ²⁶ <i>Milan</i> | 1981–1984 | 85 | 132 | 25 (29) | 3 (4) | 96 |
| Gels (1995) ²⁷ <i>Groningen</i> | 1982–1992 | 154 | 84 | 42 (27) | 2 (1) | 99 |
| Ondrus (1994) ²⁸ <i>Slovak Republic</i> | 1984–1993 | 80 | 83 | 29 (36) | 4 (5) | 95 |
| Read (1992) ²⁹ <i>United Kingdom</i> | 1984–1987 | 373 | 60 | 100 (27) | 5 (1) | 98 |
| Freedman (1987) ³⁰ <i>United Kingdom multicentre</i> | 1979–1983 | 259 | 30 | 70 (27) | 3 (1) | 98 |
| Maroto* (2005) ³¹ <i>Spanish Germ Cell Group</i> | 1994–2004 | 358 | 40 | 71 (20) | 5 (1.4) | 95 |

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| | | | | | | |
|---|-----------|------|--------|--------------|-----------|---------|
| Amato* (2004) ³² <i>MD Anderson Cancer Center, Houston</i> | 1993–1999 | 23 | 38 | 3 (13) | 0 (0) | 100 |
| Ondrus* (1998) ³³ <i>Slovak Republic</i> | 1992–1997 | 49 | 37 | 7 (14.3%) | 0 (0) | 100 |
| Pont* (1990) ³⁴ <i>Vienna</i> | 1985–1989 | 22 | 30 | 1 (4.5) | 0 (0) | 100 |
| Mortensen (2016) ³⁵ <i>Danish Testicular Cancer Study Group</i> | 1984–2007 | 1366 | 180 | 424 (31%) | 15 (1.1%) | 98.2 |
| Lago-Hernandez (2015) ³⁶ <i>Dana-Farber Cancer Institute</i> | 1997–2013 | 135 | 48 | 50 (37%) | 2 (1.5%) | NR |
| Kollmannsberger (2014) ¹⁰ <i>Multinational cohort</i> | 1998–2010 | 1139 | 62 | 221 (19%) | 5 (0.4%) | 99.4 |
| Kobayashi (2013) ³⁷ <i>Japan</i> | 1989–2008 | 36 | 99 | 9 (25%) | 0 (0%) | 100 |
| Tandstad (2009) ³⁸ <i>Sweden-Norway (Swedish-Norwegian Testicular Cancer Project)</i> | 1988–2005 | 350 | 56.4 | 44 (12.6%) | 0 (0%) | 99.9% |
| Sturgeon (2011) ³⁹ <i>Princess Margaret</i> | 1993–2005 | 371 | 75.6 | 104 (28%) | 3 (0.8%) | 99.1 |
| Pooled data | 1979–2013 | 6179 | 30–180 | 1603 (25.9%) | 67 (1.1%) | 95–100% |

*Single-arm (surveillance) of risk-adapted study. DSS: disease-specific survival.

| Supplementary Table 5. Adjuvant chemotherapy for stage I non-seminoma germ cell tumor (selected studies) | | | | | |
|---|---------------------|----------------------------|-------------------------|---------------------------------|-----------------------|
| Author (publication year) | No. patients | Risk factors | Regimen | Median followup (months) | Relapses n (%) |
| Adjuvant chemotherapy with 2 cycles of cisplatin-based combination chemotherapy | | | | | |
| Cullen (1996) ⁴⁰ | 114 | EC, LVI, no yolk sac tumor | BE ₃₆₀ P × 2 | 48 | 2 (1.7) |
| Pont (1996) ⁴¹ | 29 | LVI | BEP × 2 | 79 | 2 (6.9) |
| Chevreau (2004) ⁴² | 40 | LVI, EC | BEP × 2 | 113 | 0 (0) |
| Adjuvant chemotherapy with 1 cycle of cisplatin-based combination chemotherapy | | | | | |
| Tandstad (2009) ³⁸ | 157 | LVI | BEP × 1 | 58 | 5(3.2) |
| Tandstad (2014) ⁴³ | 258 | LVI | BEP × 1 | 95 | 8 (3.2) |
| Cullen (2020) ⁴⁴ | 246 | LVI | BEP X 1 | 49 | 7 (3.1) |

| Supplementary Table 6. Adjuvant RPLND in the management of stage I non-seminoma | | | | | | | | |
|--|-----------------------|----------------------|-----------------|------------------|-----------------------|------------------------|--------------------------------|---|
| Author (publication year) <i>Site</i> | Years of study | Patients CS I | PS I (%) | PS II (%) | Relapse PS I % | Relapse PS II % | Adjuvant chemotherapy % | No. patients dead of testis cancer (%) |
| Donohue (1993) ⁴⁵ <i>Indiana</i> | 1979–1989 | 378 | 266 (70) | 112 (30) | 12 | 34 | 13 | 3 (0.8) |
| Sweeney (2000) ⁴⁶ <i>Indiana</i> | 1990–1995 | 292 | 226 (77) | 66 (22) | 10 | 22 | 12 | 1 (0.3) |
| Nicolai (2004) ⁴⁷ <i>Milan</i> | 1985–1995 | 322 | 262 (80) | 60 (20) | NR | 27 | NR | 4 (1.2) |
| Stephenson (2005) ⁴⁸ | 1989–2002 | 297 | 214 (72) | 83 (28) | 6 | 19 | 15 | 1 (0.3) |

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| | | | | | | | | |
|--|-----------|-------------|-------------|------------|------|-------|------|---------|
| <i>MSKCC, NYC</i> | | | | | | | | |
| Spermon (2002) ⁴⁹ <i>Nijmegen</i> | 1982–1994 | 101 | 70 (69) | 31 (31) | 10 | 0 | 31 | 1 (1.0) |
| Weissbach (1990) ⁵⁰ <i>TTSB Bonn</i> | 1982–1987 | (CS1 NR) | 229 | NR | 17 | NR | NR | 2 |
| Klepp* (1997) ⁵¹ <i>SWENOTECA</i> | 1990–1994 | 99 | 85 (86) | 14 (14) | 18 | 0 | 14 | 0 (0) |
| Albers** (2008) ⁵² <i>German Testicular Cancer Study Group</i> | 1996–2005 | 173 | 141 (82) | 32 (18) | 9 | 0 | 18 | 0 (0) |
| Poulakis (2006) ⁵³ <i>Germany</i> | 2001–2004 | 50 | 39 (78%) | 11 (22%) | 2 | 0 | 22 | 0 (0) |
| Lv (2013) ⁵⁴ <i>China</i> | 1997–2011 | 34 | 19 (66%) | 15 (44%) | 11.8 | | 35 | 1 (2.9) |
| Dong (2013) ⁵⁵ <i>China</i> | 1997–2009 | 30 | 27 (90%) | 3 (10%) | 0 | 0 | 10 | 0 (0) |
| Hermans (2000) ⁵⁶ <i>Indiana</i> | 1990–1995 | 292 | 226 (77.4%) | 66 (22.6%) | 10.2 | 10.6 | 8.6 | N/A |
| Pooled data | 1979–2011 | 2068 | 77% | 33% | 9.6% | 11.3% | 17.9 | 0.65% |

**Single-arm of randomized trial.

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| Supplementary Table 7. Summary of randomized studies in advanced germ cell tumors | | | | | |
|--|-------------|--|---------------------|---|---|
| Author | Year | | No. patients | Treatment and cycles | Results: |
| Good-risk patients | | | | | |
| Bosl ⁵⁷ <i>United States</i> | 1988 | | 164 | EP × 4 VAB-6 × 3 | No difference EP less toxic |
| Einhorn ⁵⁸ <i>Indiana</i> | 1989 | | 184 | BEP × 3 BEP × 4 | No difference BEP × 3 less toxic |
| de Wit ⁵⁹ <i>EORTC/MRC</i> | 2001 | | 812 | BEP × 3 BEP × 3, EP X1 | No difference BEP × 3 less toxic |
| Toner ⁶⁰ <i>Australia/New Zealand</i> | 2001 | | 166 | BE500P X 3 BE360PX4 | BE500P superior OS |
| Role of bleomycin | | | | | |
| Levi ⁶¹ <i>Australia</i> | 1993 | | 218 | PVB X 2-6 PV X 2-7 | PVB:less cancer deaths but more toxicity deaths |
| Loehrer ⁶² <i>ECOG</i> | 1995 | | 171 | BEP × 3 EP × 3 | BEP × 3 superior |
| de Wit ⁶³ <i>EORTC</i> | 1997 | | 395 | BE ₃₆₀ P × 4 E ₃₆₀ P × 4 | BE360P: RR higher |
| Culine ⁶⁴ <i>GETUG</i> | 2007 | | 270 | BEP × 3 EP × 4 | RR similar BEP X 3: EFS and OS underpowered but nonsignificant trend |
| Role of carboplatin (good risk) | | | | | |
| Bajorin ⁶⁵ <i>United States</i> | 1993 | | 265 | EP × 4 E Carbo × 4 | EP × 4 superior |
| Bokemeyer ⁶⁶ <i>Germany</i> | 1996 | | 54 NSGCT | BE500P X 3 BE360Carbo X 4 | BEP superior with lower relapses |
| Horwich ⁶⁷ <i>MRC/EORTC</i> | 1997 | | 598 NSGCT | BE360P × 4 BE360Carbo × 4 | BE ₃₆₀ P × 4 superior |
| Horwich ⁶⁸ <i>MRC</i> | 2000 | | 130 SEMINOMA | EP X 4 Carbo X 4 | Closed early. EP still standard |
| Intermediate- and poor-risk | | | | | |
| Williams ⁶⁹ <i>Indiana</i> | 1987 | | 261 | BEP X 4 PVB X 4 | BEP is superior |
| Nichols ⁷⁰ | 1991 | | 159 | BEP X 4 BEP200 X 4 | No difference BEP less toxic |

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| | | | | |
|---|------|--|----------------------------|---|
| <i>SWOG/Southeastern Cancer Study Group</i> | | | | |
| De Wit ⁷¹ <i>EORTC</i> | 1995 | | 234 | BEP X 4 PVB/BEP X4 No difference BEP less toxic |
| Nichols ⁷² <i>ECOG/SWOG/CALGB</i> | 1998 | | 286 | BEP × 4 VIP × 4 No difference BEP less toxic |
| de Wit ⁷³ <i>EORTC</i> | 1998 | | 84 | BEP × 4 VIP × 4 No difference BEP less toxic (closed early) |
| Kaye ⁷⁴ <i>MRC/EORTC</i> | 1998 | | 371 | BEP X 4 + EP X2 BOP X 3+ VIPB X 3 No difference BEP X 4 + EP X 2 less toxic |
| Droz ⁷⁵ <i>GETUG</i> | 2007 | | 115 | BEPVin × 4 BEPVin + HDCT No difference BEPVin less toxic |
| Motzer ⁷⁶ <i>MSKCC/ECOG/SWOG/ CALGB</i> | 2007 | | 219 | BEP × 4 BEP + HDCT No difference BEP less toxic |
| Daugaard ⁷⁷ <i>EORTC/Germany/Spain</i> | 2011 | | 131 | BEP X 4 VIPX 1 + HDCT X 3 No difference RR and OS HDCT: nonsignificant trend in FFS |
| de Wit ⁷⁸ <i>EORTC/MRC/Germany /Spain</i> | 2012 | | 337 | BEP x 4 T-BEP x4 No difference (closed early) |
| Fizazi ⁷⁹ <i>GETUG/MDAnderson</i> | 2014 | | 263 (203 randomized) | BEP x 4 BEP X 1 + Dose Dense chemo X 4 Dose dense superior in PFS (primary endpoint), not OS |

[#]Dose-dense: BEP + paclitaxel+oxaliplatin X 2 cycles and then cisplatin+ ifosfamide+bleomycin X 2 cycles with G-CSF support. AGCTG: Australasian Germ Cell Trial Group; BECarbo: bleomycin, etoposide, and carboplatin; BEP: bleomycin, etoposide, cisplatin; BEPVin: bleomycin + etoposide + cisplatin + vinblastine; BOP: bleomycin, vincristine, cisplatin; cisplatin+VIP: cisplatin + ifosfamide + etoposide; dose-dense chemo: T-BEP+ Oxaliplatin X 2 then cisplatin, bleomycin ifosfamide X 2; ECarbo: etoposide and carboplatin; EORTC: European Organization for Research and Treatment of Cancer; EP: etoposide and cisplatin; EPVin: etoposide + cisplatin + vinblastine; FFS: failure-free survival; HDCT: high-dose chemotherapy; IGCCCG: International Germ Cell Consensus Classification; MRC: Medical Research Council; GTCG: German Testicular Cancer Group; MSKCC: Memorial Sloan-Kettering Cancer Center; OS: overall survival; PFS: progression-free survival; PVB: cisplatin , vinblastine, bleomycin; PV: vinblastine + cisplatin; RR: response rate; T-BEP: paclitaxel+cisplatin+etoposide+bleomycin; VAB-6: vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin; VIP: etoposide ifosfamide cisplatin.

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