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eTable 1: ENSAT staging

|  |
| --- |
| European Network for the Study of Adrenal Tumors staging system |
| Stage | TNM |
| I | T1 N0 M0 |
| II | T2 N0 M0 |
| III | T1-2 N1 M0T3-4 N0-1 M0 |
| IV | any M1 |

eFigure 1: Sensitivity analysis 1, overall survival with 2:1 matching

Overall survival of adrenocortical carcinoma patients treated with or without adjuvant radiotherapy, sensitivity analysis matching one adjuvant radiotherapy case to up to two control cases where possible.



eFigure 2: Sensitivity analysis 1, local recurrence-free survival with 2:1 matching

Local recurrence-free survival of adrenocortical carcinoma patients treated with or without adjuvant radiotherapy, sensitivity analysis matching one adjuvant radiotherapy case to up to two control cases where possible.



eFigure 3: Sensitivity analysis 1, all recurrence-free survival with 2:1 matching

All recurrence-free survival of adrenocortical carcinoma patients treated with or without adjuvant radiotherapy, sensitivity analysis matching one adjuvant radiotherapy case to up to two control cases where possible.



eTable 2: Sensitivity analysis 2, sample characteristics of Immortal Time Bias Analysis

Sample characteristics of immortal time bias analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|   | No radiation therapy | Radiation therapy | p-value |
| (N=39) | (N=39) |
| Sex: N (%) |  |  |  |
| Males | 19 (48.7) | 18 (46.2) | 0.808a,c |
| Females | 20 (51.3) | 21 (53.9) |  |
| Age in years: | 44.9 (18 – 69) | 47.1 (13 – 74) | 0.699b,c |
| Mean (Min. – Max.) |
| Disease stage |  |  |  |
| I | 2 (5.1) | 2 (5.7) | 0.795a,c |
| II | 15 (38.5) | 16 (41.0) |  |
| III | 21 (53.9) | 18 (44.9) |  |
| IV | 1 (2.6) | 3 (7.7) |  |
| Mitotane Use |  |  |  |
| Yes | 28 (71.8) | 30 (76.9) | 0.617a |
| No | 11 (28.2) | 9 (23.1) |  |
| Tumor Grade |  |  |  |
| Low | 7 (18.0) | 10 (25.6) | 0.317a,c |
| High | 32 (82.0) | 29 (74.4) |  |
| Tumor Size (cm): | 11.7 (4.1 – 23.0) | 10.4 (0.6 – 22.5) | 0.077b |
| Mean (Min. – Max., cm) |
| Hormone production (any) |  |  |  |
| No | 19 (48.7) | 19 (48.7) | 0.158a |
| Yes | 20 (51.3) | 20 (51.3) |  |
| Not reported | 0 | 5 (12.8) |  |
| Cortisol production |  |  |  |
| No | 26 (66.7) | 21 (53.9) | 0.156a |
| Yes | 13 (33.3) | 13 (33.3) |  |
| Not reported | 0 | 5 (12.8) |  |
| Surgical Margins |  |  |  |
| Negative | 24 (61.5) | 30 (76.9) | 0.428a,c |
| Positive | 7 (18.0) | 5 (12.8) |  |
| Not reported | 8 (20.5) | 4 (10.3) |  |
| aMcNemar’s test of dependent proportion or Bowker’s test of symmetry. |
| bPaired t-test. |
| cAccounted for in the model calculating the propensity weights for adjuvant radiotherapy. |

eFigure 4: Sensitivity analysis 2, overall survival with immortal time bias

The overall survival distribution for cases and controls was significantly different (log-rank p = 0.0029). The 5-year survival estimate for patients with RT was 72.1%, 95% CI: 49.2 – 86.0 and for patients without was 37.1%, 95% CI: 19.8 – 54.6. If we use a cox proportional hazard models, adjusting for any mitotane use, then the hazards ratio is 2.98, 95% CI: 1.33 – 6.68, p = 0.0082.

eFigure 5: Sensitivity analysis 2, local recurrence-free survival with immortal time bias

The local recurrence-free survival distribution for significantly higher cases then controls (log-rank p-value 0.0075). The 5-year survival estimate for patients with RT was 53.5%, 95% CI: 32.2 – 70.8 and for patients without was 26.6%, 95% CI: 12.1 – 43.6. If we use a cox proportional hazard models, adjusting for any mitotane use, the hazards ratio is 2.29, 95% CI: 1.17 – 4.46, p = 0.0154.



eFigure 6: Sensitivity analysis 2, all recurrence-free survival with immortal time bias

The recurrence-free survival distribution for significantly higher cases then controls (log-rank p-value 0.0059). The 5-year survival estimate for patients with RT was 46.7%, 95% CI: 26.9 – 64.3 and for patients without was 19.7%, 95% CI: 7.5 – 36.2. If we use a cox proportional hazard models, adjusting for any mitotane use, the hazards ratio is 2.15, 95% CI: 1.16 – 3.99, p = 0.0153.



eTable 3: Sensitivity analysis 3, sample characteristics of sensitivity analysis matching by initial stage

|  |  |  |  |
| --- | --- | --- | --- |
|  | No radiation therapy(N=39) | Radiation therapy(N=39) | P-value |
| Sex: N (%) |  |  |  |
|  Males | 18 (46.2) | 18 (46.2) | 1a,c |
|  Females | 21 (53.9) | 21 (53.9) |  |
| Age in years:Mean (Min. – Max.) | 45.6 (18 – 80) | 47.1 (13 – 74) | 0.527b,c |
| Disease stage |  |  |  |
|  I | 2 (5.1)  | 2 (5.1) | 0.809a,c |
|  II | 16 (41.0) | 16 (41.0) |  |
|  III | 15 (38.5) | 18 (46.2) |  |
|  IV | 6 (15.4) | 3 (7.7) |  |
| Mitotane Use |  |  |  |
|  Yes | 29 (74.4) | 30 (76.9) | 0.782a |
|  No | 10 (25.6) | 9 (23.1) |  |
| Tumor Grade |  |  |  |
|  Low | 12 (30.8) | 10 (25.6) | 0.317a,c |
|  High | 27 (69.2) | 29 (74.4) |  |
| Size in cm:Mean (Min. – Max.) | 12.1 (4.1 – 20.0) | 10.4 (0.6 – 22.5) | 0.065b |
| Hormone production (any) |  |  |  |
|  Yes | 19 (48.7) | 15 (38.5) | 0.152a |
|  No | 20 (51.3) | 19 (48.7) |  |
|  Not reported | 0  | 5 (12.8) |  |
| Cortisol production |  |  |  |
|  Yes | 13 (33.3%) | 13 (33.3) | 0.152a |
|  No | 26 (66.7) | 21 (53.9) |  |
|  Not reported | 0 | 5 (12.8) |  |
| Surgical Margins |  |  |  |
|  Negative | 31 (79.5) | 30 (76.9) | 0.343a,c |
|  Positive | 2 (5.1) | 5 (12.8) |  |
|  Not reported | 6 (15.4) | 4 (10.3) |  |
| aMcNemar’s test of dependent proportion or Bowker’s test of symmetry.bPaired t-test.cAccounted for in the model calculating the propensity weights for adjuvant radiotherapy. |

eFigure 7: Sensitivity analysis 3, overall survival with comparison with initial stage matched at diagnosis

The overall survival distribution for cases and controls was significantly different (log-rank p = 0.0054). The 5-year survival estimate for patients with RT was 72.1%, 95% CI: 49.2 – 86.0 and for patients without was 28.1%, 95% CI: 6.9 – 54.6. If we use a cox proportional hazard models, adjusting for any mitotane use, then the hazards ratio is 3.23, 95% CI: 1.37 – 7.63, p = 0.008.



eFigure 8: Sensitivity analysis 3, local recurrence-free survival with initial stage matched at diagnosis

The local recurrence-free survival distribution was significantly higher for cases than controls (log-rank p-value 0.0024). The 5-year local recurrence-free survival estimate for patients with RT was 53.5%, 95% CI: 32.2 – 70.8 and for patients without was 21.1%, 95% CI: 1.9 – 54.1. If we use a cox proportional hazard models, adjusting adjusting for any mitotane use, the hazards ratio is 2.19, 95% CI: 1.09–4.42, p = 0.028.



eFigure 9: Sensitivity analysis 3, all recurrence-free survival with iniital stage matched at diagnosis

The recurrence-free survival distribution was higher, but not significantly, for cases than controls (log-rank p-value 0.128). The 5-year survival estimate for patients with RT was 46.7%, 95% CI: 26.9 – 64.3 and for patients without was 22.0%, 95% CI: 2.0 – 55.9. If we use a cox proportional hazard models, adjusting for any mitotane use, the hazards ratio is 1.68, 95% CI: 0.86 – 3.28, p = 0.127.

