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Adrenal metastasectomy for oligometastatic non–small cell lung cancer in the era of immunotherapy and molecular-targeted therapy: outcomes and application of the ESTRO-EORTC oligometastatic classification in a single-institution surgical cohort

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Adrenal metastasectomy for oligometastatic non–small cell lung cancer in the era of immunotherapy and molecular-targeted therapy: outcomes and application of the ESTRO-EORTC oligometastatic classification in a single-institution surgical cohort

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Abstract

Background Adrenal metastasectomy for non–small cell lung cancer (NSCLC) has been reported mainly in historical series, and the ESTRO-EORTC oligometastatic classification has rarely been applied to surgical cohorts. We evaluated contemporary outcomes and applied this classification to a surgical adrenal cohort.

Methods Consecutive patients who underwent adrenal metastasectomy for NSCLC at a single institution between 2011 and 2025 were retrospectively reviewed; small cell carcinoma and non-lung primary tumors were excluded. Overall, cancer-specific, recurrence-free, and post-recurrence survival were estimated by the Kaplan–Meier method. Each patient was assigned an ESTRO-EORTC category, and post-recurrence systemic therapy was recorded.

Results Twenty-eight patients were analyzed (adenocarcinoma 79%; 61% operated in 2020 or later). Surgery was minimally invasive in 86%, with one Clavien–Dindo grade II event (blood transfusion), no grade ≥III complication, and no 30-day mortality. Three-year overall survival was 60% and three-year cancer-specific survival 66%, whereas median recurrence-free survival was 5.6 months (2-year 25%) with recurrence in 75%; median post-recurrence survival was 32.1 months. Among 21 patients with recurrence, 18 (86%) received post-recurrence systemic therapy. In an exploratory comparison, oligorecurrence (n=16) was associated with longer recurrence-free survival than all other ESTRO-EORTC states combined (n=12; median 15.1 vs 3.7 months; hazard ratio 0.29, 95% confidence interval 0.12–0.71; log-rank p=0.004).

Conclusions Adrenal metastasectomy for NSCLC was safe and, despite frequent recurrence, was followed by prolonged survival in a highly selected cohort with frequent use of contemporary post-recurrence systemic therapy. Oligorecurrence was associated with longer recurrence-free survival than the other ESTRO-EORTC states combined.

Keywords Adrenal metastasectomy · Non–small cell lung cancer · Oligometastatic disease · ESTRO-

EORTC classification · Immunotherapy

Introduction

The adrenal gland is one of the most frequent sites of distant metastasis from lung cancer, and resection of an isolated adrenal metastasis has been performed with curative intent in carefully selected patients [1–3]. Across large surgical series, 5-year overall survival after adrenal metastasectomy has ranged from approximately 31% to 43% [1–4], and a systematic review of predominantly single-arm series estimated a 5-year survival of about 28% [5]. Non-radical resection, larger tumor size, and concomitant extra-adrenal disease [1, 2, 4], contralateral location [2], and nodal involvement of the primary tumor [5, 6] have been reported as adverse prognostic factors. Our institution previously reported a smaller series of 14 patients with solitary adrenal metastasis from lung cancer [7].

These surgical series, however, accrued patients before immune checkpoint inhibitors and next-generation targeted agents entered routine use, with accrual generally closing no later than 2018 [1–6]. Over the past decade, systemic therapy for advanced non–small cell lung cancer (NSCLC) has been transformed: immune checkpoint inhibitors and driver-directed agents targeting EGFR, ALK, and other alterations have substantially prolonged survival even after distant recurrence, and local ablative therapy—including surgery and stereotactic body radiotherapy—has been increasingly integrated into the management of oligometastatic disease. In this contemporary context, systemic therapy can achieve durable disease control even after recurrence. How adrenal metastasectomy performs in this setting has not been characterized in a dedicated NSCLC surgical cohort.

In parallel, the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) consensus established a common nomenclature for oligometastatic disease based on prior polymetastatic history (genuine vs induced), prior oligometastatic history (de novo vs repeat), chronicity (synchronous vs metachronous), and the relationship to systemic therapy (oligorecurrence, oligoprogression, oligopersistence) [8]. The prognostic value of this classification has been validated, but its development and validation have taken place almost exclusively in radiotherapy cohorts [9, 10]; to the best of our knowledge, it has not been applied to a surgical adrenal

metastasectomy cohort.

We therefore evaluated the perioperative and oncological outcomes of adrenal metastasectomy for oligometastatic NSCLC in the contemporary era, characterized the cohort with the ESTRO-EORTC classification, and examined post-recurrence systemic therapy to interpret the relationship between recurrence and survival.

Patients and methods

Patient selection

We reviewed the medical records of consecutive patients who underwent adrenal metastasectomy at our department (National Cancer Center Hospital East, Chiba, Japan) between 2011 and 2025. Of 44 consecutive adrenal metastasectomies, 30 were performed for lung cancer; 2 patients with small cell carcinoma were excluded because of its distinct biology and its status as a relative contraindication [2], leaving 28 patients with NSCLC for analysis. All operations were performed by the urologic surgical team. The present cohort partially overlaps with the patients in our previous report [7].

Surgical technique

Adrenal metastasectomy was performed by a minimally invasive approach—transperitoneal laparoscopic surgery or gasless minimum incision endoscopic surgery (MIES)—whenever feasible, converting to open surgery when required. The renal parenchyma and the psoas muscle were used as landmarks, and the gland was mobilized posteriorly to allow safe circumferential dissection.

Data collection and definitions

Collected variables included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, histology, driver alteration and programmed death-ligand 1 (PD-L1) tumor proportion score, clinical T, N, and M categories (TNM 8th edition), tumor laterality relative to the primary tumor (ipsilateral vs. contralateral), concomitant extra-adrenal metastasis, tumor size, surgical approach, operative time, estimated blood loss, resection margin, Clavien–Dindo complication grade, and hospital length of stay. The disease-free interval was defined as the interval from primary tumor diagnosis to adrenal metastasis diagnosis. Recurrence was defined as radiological or pathological evidence of new or progressive disease after adrenalectomy and was classified as adrenal-bed (local) or distant. Two patients had concomitant extra-adrenal disease at adrenalectomy and were therefore not rendered disease-free; in these patients, progression of the known extra-adrenal lesions was also counted as an event. Post-recurrence systemic

therapy was recorded for all patients with recurrence and categorized as immune checkpoint inhibitor, molecular-targeted agent, or cytotoxic chemotherapy, with the number of sequential treatment lines.

ESTRO-EORTC classification

Each patient was assigned an ESTRO-EORTC oligometastatic category according to the consensus definitions [8]. The polymetastatic history (genuine vs induced) and the disease state at the time of adrenal metastasis detection (oligorecurrence during a treatment-free interval, or oligoprogression/oligopersistence during active systemic therapy for known advanced disease) were determined from the treatment timeline; presentation was classified as synchronous when the adrenal metastasis was detected within 6 months of primary tumor diagnosis or at the first restaging after curative-intent treatment without an intervening disease-free interval, and as metachronous otherwise.

Endpoints and statistical analysis

Overall survival (OS) was measured from adrenalectomy to death from any cause or last follow-up; cancer-specific survival (CSS) to death from lung cancer, censoring non-cancer deaths; recurrence-free survival (RFS) to first recurrence or death; and post-recurrence survival (PRS) from first recurrence to death or last follow-up. Continuous variables are presented as the median [interquartile range] and categorical variables as n (%). Survival was estimated by the Kaplan–Meier method and compared by the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by univariable Cox regression. Survival times were calculated in days and converted to months (1 month = 30.44 days), and median follow-up was estimated by the reverse Kaplan–Meier method. Given the limited number of events, analyses were descriptive and univariable; multivariable modeling was not undertaken. Because multiple univariable subgroup comparisons were performed without correction for multiple testing, these analyses are exploratory and hypothesis-generating. A two-sided $p < 0.05$ was considered significant. Statistical analyses were performed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The study was approved by the National Cancer Center Institutional Review Board (2018-159).

Results

Patient characteristics

Twenty-eight patients were analyzed (Table 1). The median age was 68.5 years, and 20 (71%) were men. Histology was adenocarcinoma in 22 (79%), squamous cell carcinoma in 2, NSCLC not otherwise specified in 2, sarcomatoid carcinoma in 1, and large cell carcinoma in 1. Seventeen patients (61%) were operated in 2020 or later. A driver alteration was present in 9 patients (EGFR in 5, KRAS in 2, ALK in 1, other in 1), 14 were wild-type, and 5 were untested; PD-L1 was tested in 14 (50%). The clinical nodal category of the primary was N0 in 12 and N+ in 16. At the time of adrenalectomy the metastasis was ipsilateral in 19 and contralateral in 9, and was isolated in 26 while 2 patients had concomitant extra-adrenal disease. The median tumor size was 24 mm and the median disease-free interval was 13.5 months.

ESTRO-EORTC classification

Twenty-four patients had genuine and 4 had induced oligometastatic disease. The categories were de novo metachronous oligorecurrence in 16, de novo synchronous disease in 6, de novo metachronous oligoprogression in 2, induced oligoprogression in 3, and induced oligopersistence in 1 (Table 2). By disease state, 16 were oligorecurrence, 5 oligoprogression, 1 oligopersistence, and 6 synchronous.

Perioperative outcomes

The approach was laparoscopic in 18, gasless minimum incision endoscopic surgery (MIES) in 6, and open in 2, with conversion in 2; a minimally invasive approach was completed in 24 (86%). The median operative time was 130 minutes [84–164] and the median estimated blood loss was 18 mL [9–70]. Resection was R0 in 23, R1 in 4, and R2 in 1. One patient, who required conversion to open surgery with concomitant resection, had an estimated blood loss of 1,623 mL and received 4 units of red blood cells (Clavien–Dindo grade II); no grade ≥III complication or 30-day mortality occurred, and the median hospital stay was 6 days. One patient died of pneumonia unrelated to surgery on postoperative day 57 (90-

day mortality, 3.6%).

Survival

At a median follow-up of 41.1 months (interquartile range 20.7–78.0) estimated by the reverse Kaplan–Meier method, 12 patients had died (9 from lung cancer, 3 from other causes). The 1- and 3-year OS rates were 85% (95% CI 65–94%) and 60% (95% CI 36–77%), respectively (Fig. 1a), and the corresponding CSS rates were 88% and 66%. Because only 10 patients remained at risk at 3 years, estimates beyond 3 years are not reported. In contrast, the median RFS was only 5.6 months (95% CI 3.7–16.7; 23 events), with 1- and 2-year rates of 37% and 25% (Fig. 1b); recurrence occurred in 21 patients (75%) and was distant in 19 and confined to the adrenal bed in 2. The median PRS was 32.1 months.

Post-recurrence systemic therapy

Among the 21 patients with recurrence, 18 (86%) received post-recurrence systemic therapy (Table 3). This included an immune checkpoint inhibitor in 8 patients and a molecular-targeted agent (EGFR- or ALK-directed) in 6, while 13 received cytotoxic chemotherapy; 7 patients received two or more sequential lines of therapy, and 5 additionally underwent local therapy (stereotactic radiosurgery or radiotherapy) for recurrent or oligoprogressive sites. The molecular-targeted regimens spanned successive generations of therapy, including osimertinib, alectinib, and later-line agents such as amivantamab with lazertinib.

Prognostic factors

In an exploratory comparison, oligorecurrence had a longer RFS (median 15.1 months) than the other states combined (median 3.7 months; HR 0.29, 95% CI 0.12–0.71; log-rank p = 0.004; Fig. 2). The single patient with oligopersistence died of a non-cancer cause without recurrence, which was counted as an RFS event. Longer RFS was also associated with ipsilateral versus contralateral disease (median 9.9 vs 4.7 months; HR 0.38, 95% CI 0.15–0.99; p = 0.041); both patients with concomitant extra-adrenal disease recurred. No clear association was observed for induced versus genuine disease (OS HR for induced

disease 0.78, 95% CI 0.10–6.18; p = 0.81) or clinical N0 disease (RFS HR 0.68, 95% CI 0.29–1.59; p = 0.37). The 2-year OS was similar in patients operated in 2020 or later and earlier (80% vs 82%), and RFS did not differ by era; this comparison is limited by the shorter follow-up of the recent group.

Discussion

In this contemporary single-institution cohort, adrenal metastasectomy for oligometastatic NSCLC was performed safely, with no major complication and no 30-day mortality. Because no comparison group of patients managed without resection was available, the survival observed here cannot be attributed to metastasectomy itself. The defining finding was a dissociation between early, frequent recurrence (median RFS 5.6 months; recurrence in 75%) and a 3-year OS of 60%, with a median post-recurrence survival of 32.1 months.

One possible explanation for this dissociation is contemporary systemic therapy. Whereas historical series accrued patients before the routine use of immune checkpoint inhibitors and next-generation targeted agents [1–6], 61% of our patients were operated in 2020 or later, and a driver alteration was identified in one-third. Critically, among the 21 patients with recurrence, 18 (86%) received post-recurrence systemic therapy, including immune checkpoint inhibitors in 8 and molecular-targeted agents in 6, and 7 received two or more sequential lines. This indicates that recurrence in this cohort was commonly managed with contemporary systemic therapy rather than representing a terminal event, which may have contributed to the prolonged post-recurrence survival, although response to these agents was not formally assessed. Alternatively, the adrenal gland has been identified as a low-risk site of recurrence that does not shorten post-recurrence survival in resected NSCLC [11], suggesting that the survival observed here may also reflect the biology of adrenal-limited disease. Together, these observations position adrenal resection as one component of multidisciplinary management—achieving durable local control and pathological confirmation—rather than a stand-alone cure.

Applying the ESTRO-EORTC classification—to our knowledge, the first such application in a surgical adrenal metastasectomy cohort—provided an exploratory framework. In the pooled comparison, oligorecurrence, in which the adrenal metastasis appears during a treatment-free interval, was associated with longer RFS (median 15.1 months) than the other states combined (median 3.7 months; log-rank $p = 0.004$). Oligoprogression had a median RFS of 4.1 months, whereas the oligopersistence subgroup

comprised only one patient, who died of a non-cancer cause without recurrence. These observations are consistent with radiotherapy-based validations, in which oligoprogression and induced states carried the worst prognosis; in a 385-patient single-center stereotactic body radiotherapy (SBRT) cohort, induced oligometastatic disease had the shortest overall survival, and in the phase II SABR-5 trial the classification independently predicted progression-free and overall survival, with chronicity and oligoprogression the dominant factors [9, 10]. By contrast, synchronous presentation, which predicted longer survival in SABR-5 [10], was associated with short RFS in our cohort. The present findings suggest that the classification may also be informative after surgery, although the small numbers of oligopersistence (n = 1) and synchronous (n = 6) cases warrant caution. In contrast to radiotherapy cohorts, in which induced and oligoprogression states are common, our surgical cohort was enriched for de novo oligorecurrence (57%), reflecting the selection of patients with an isolated, metachronous adrenal metastasis for resection [9]. This distribution also highlights the heterogeneity of the cohort, which spanned classic isolated adrenal metastasectomy and resection of an oligoprogressive adrenal site in patients with previously polymetastatic but subsequently controlled disease.

Our anatomical findings are concordant with prior surgical series. Ipsilateral location was associated with longer RFS, in keeping with a multi-institutional lung cohort in which ipsilateral metastases independently predicted longer disease-free and overall survival (hazard ratios 0.13 and 0.55) [2], and is consistent with the hypothesis of a lymphatic route of retroperitoneal spread for ipsilateral disease with a more aggressive hematogenous process for contralateral disease. The adverse effect of concomitant extra-adrenal disease, although based on only two patients in our cohort, is consistent with prior series that identified extra-adrenal metastases and non-radical resection as adverse factors [1, 2, 4]. Whereas some series identified mediastinal nodal involvement of the primary as a dominant factor [6], we observed no clear association for clinical N0 disease, likely reflecting limited statistical power.

From a technical standpoint, adrenal metastasectomy was accomplished with a median blood loss of 18 mL and no major morbidity, underscoring the safety of a minimally invasive approach. Stereotactic body

radiotherapy achieves high local control of adrenal metastases (1- to 2-year local control approximately 80–85%) [12] and is an appropriate alternative for patients who are unfit for or decline surgery; resection additionally provides pathological confirmation and single-session local control, and its role relative to radiotherapy warrants prospective comparison.

Our study has several limitations. First, this retrospective, single-institution study had a small sample size with few events, precluding multivariable adjustment; the univariable associations are exploratory and subject to confounding by indication. Second, accrual spanned 2011 to 2025, the median follow-up was 41.1 months, and only 7 patients were observed beyond 5 years; estimates beyond 3 years are therefore not reported, and the era comparison must be interpreted cautiously. Third, PD-L1 was untested in about half of the cohort and molecular profiling evolved over time, limiting inference about biomarker-defined subgroups. Fourth, assignment of ESTRO-EORTC categories from retrospective records is subject to interobserver variability, and surgical selection and imaging assessment may bias the results.

In conclusion, adrenal metastasectomy for oligometastatic NSCLC was safe and, despite early and frequent recurrence, was followed by prolonged survival in the contemporary treatment era, in a cohort in which post-recurrence systemic therapy was frequently used. In an exploratory analysis, oligorecurrence was associated with longer RFS than the other ESTRO-EORTC states combined. A large-scale prospective study is warranted to define the role of adrenal metastasectomy within multidisciplinary care in the immunotherapy and molecular-targeted era.

Statements and Declarations

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Conflict of interest Yu Tanaka reports research funding paid to the institution from Bristol Myers Squibb K.K., AstraZeneca K.K., D3 Bio (Wuxi) Co., Ltd., Takeda Pharmaceutical Company Limited, MSD K.K., Chugai Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K.; honoraria for lectures from Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Janssen Pharmaceutical K.K., Merck KGaA (Darmstadt, Germany), Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., and MSD K.K.; and manuscript fees from Taiho Pharmaceutical Co., Ltd., all outside the submitted work. The other authors declare no conflict of interest.

Ethics approval This retrospective study was approved by the National Cancer Center Institutional Review Board (2018-159) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate The requirement for written informed consent was waived owing to the retrospective design; patients were given the opportunity to opt out.

Consent for publication Not applicable.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions Tomoki Kimura: conceptualization, data curation, formal analysis, writing—original draft. Shugo Yajima: conceptualization, supervision, writing—review and editing. Takaharu Hamada, Shota Umezawa, Gaku Okumura, Shu Gozu, Madoka Kataoka: data curation, writing—review and editing. Yasukazu Nakanishi: supervision, writing—review and editing. Yu Tanaka: writing—review and editing. Hitoshi Masuda: supervision, writing—review and editing.

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Table 1 Patient, tumor, and perioperative characteristics (n = 28)

Variable	Value
Age, years, median (range)	68.5 (50–76)
Male, n (%)	20 (71)
Histology: adenocarcinoma / squamous / NOS / sarcomatoid / large cell	22 / 2 / 2 / 1 / 1
Operated 2020 or later, n (%)	17 (61)
Driver alteration (EGFR / KRAS / ALK / other), n	9 (5 / 2 / 1 / 1)
PD-L1 tested / TPS ≥50%, n	14 / 6
ECOG PS 0 / 1, n	23 / 5
Clinical N0 / N+, n	12 / 16
Ipsilateral / contralateral, n	19 / 9
Isolated / with extra-adrenal disease, n	26 / 2
Tumor size, mm, median [IQR]	24 [19–32]
Disease-free interval, months, median [IQR]	13.5 [8–26]
ESTRO-EORTC genuine / induced, n	24 / 4
Approach: laparoscopic / MIES / open / converted, n	18 / 6 / 2 / 2
Operative time, min, median [IQR]	130 [84–164]
Estimated blood loss, mL, median [IQR]	18 [9–70]
Margin R0 / R1 / R2, n	23 / 4 / 1
Clavien–Dindo grade II (transfusion) / ≥III / 30-day / 90-day mortality, n	1 / 0 / 0 / 1
Length of stay, days, median	6

Table 2 ESTRO-EORTC disease states and outcomes

Disease state	n	Median RFS (mo)	Deaths, n
Oligorecurrence	16	15.1	6
Oligoprogression	5	4.1	1
Oligopersistence	1	—[a]	1
Synchronous (de novo)	6	3.3[a]	4[a]

RFS values are medians; deaths are numbers of patients. Genuine 24 / induced 4. [a]For oligopersistence (n=1), the median was not reported; the patient did not recur and died of a non-cancer cause at 24.6 months, which was counted as an RFS event. Synchronous (n=6) values are based on few patients and shown descriptively.

Table 3 Post-recurrence systemic therapy (patients with recurrence, n = 21)

Post-recurrence therapy	n (%)
Any systemic therapy	18 (86)
Immune checkpoint inhibitor	8
Molecular-targeted agent (EGFR/ALK)	6
Cytotoxic chemotherapy	13
≥2 sequential lines	7
Local therapy (SRS/RT) for recurrence or oligoprogression	5
No systemic therapy (local therapy only / none)	3 (1 / 2)

Categories are not mutually exclusive. One patient with EGFR wild-type disease received erlotinib as a later-line therapy. RT, radiotherapy; SRS, stereotactic radiosurgery

Figure legends

Fig. 1 Kaplan–Meier estimates of overall survival (a) and recurrence-free survival (b) after adrenal metastasectomy (n = 28). Tick marks indicate censored observations; numbers below the plots indicate patients at risk; the x-axis is truncated at 36 months, when 10 (overall survival) and 5 (recurrence-free survival) patients remained at risk

Fig. 2 Recurrence-free survival in an exploratory comparison of oligorecurrence versus all other ESTRO-EORTC disease states (hazard ratio 0.29, 95% confidence interval 0.12–0.71; log-rank p = 0.004). The solid and dashed lines represent oligorecurrence and other states, respectively; tick marks indicate censored observations; numbers below the plot indicate patients at risk; the x-axis is truncated at 36 months

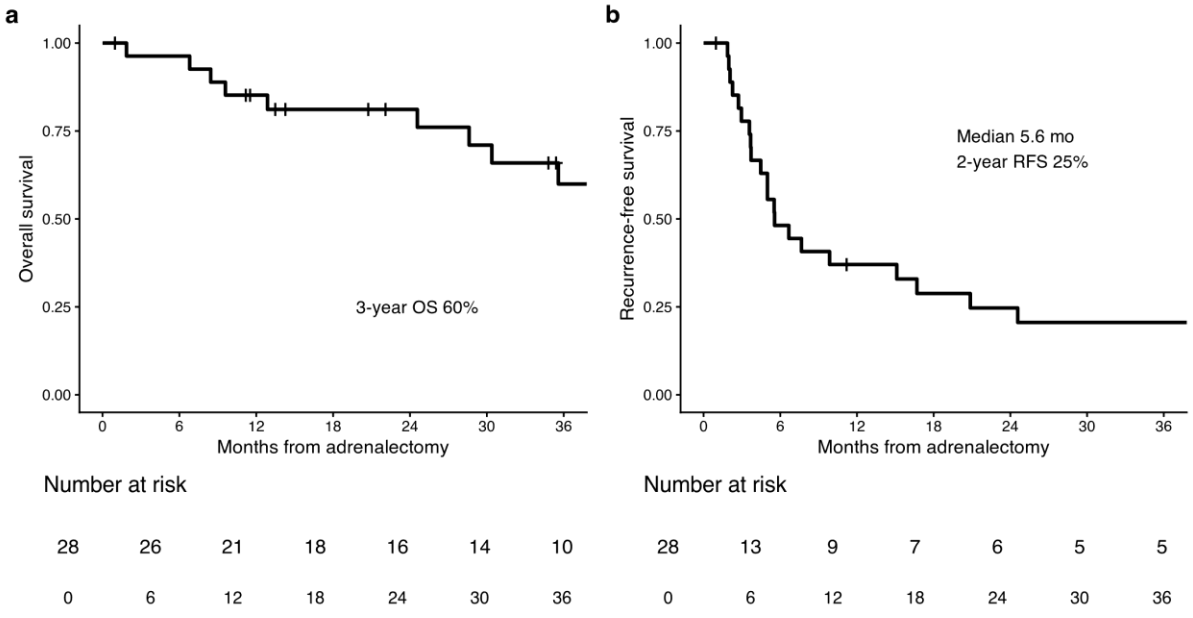


Fig. 1

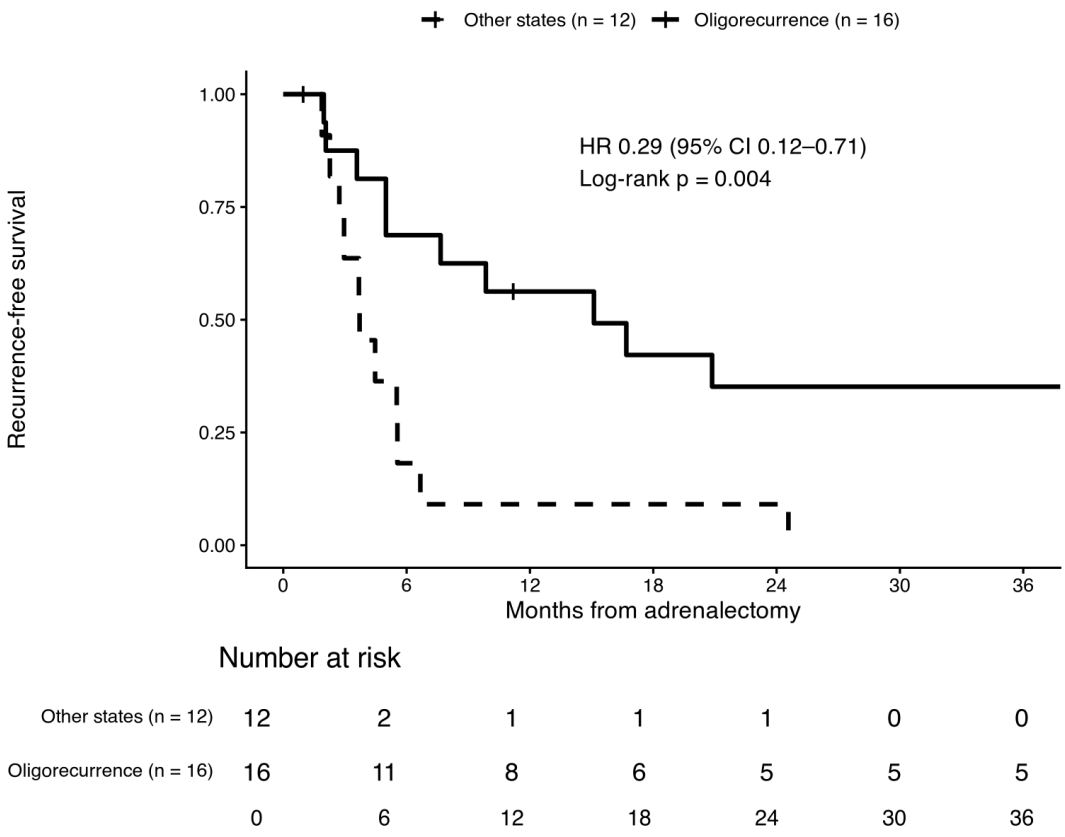

Other states (n = 12)
Oligorecurrence (n = 16)
Recurrence-free survival
1.00
0.75
0.50
0.25
0.00
HR 0.29 (95% CI 0.12–0.71)
Log-rank p = 0.004
0
6
12
18
24
30
36
Months from adrenalectomy
Number at risk
Other states (n = 12) 12 2 1 1 1 0 0
Oligorecurrence (n = 16) 16 11 8 6 5 5 5
0 6 12 18 24 30 36

Fig. 2