Supplementary Online Content

Gensheimer MF, Gee H, Shirato H, et al. Individualized stereotactic ablative radiotherapy for treating lung tumors: the iSABR phase 2 nonrandomized controlled trial. Published online September 14, 2023. *JAMA Oncol*. doi:10.1001/jamaoncol.2023.3495

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Treatment plan data, grouped by assigned dose. Data are expressed as: median (25^{th} percentile, 75^{th} percentile).

Parameter	All dose levels (n=285)	25 Gy in 1 fraction (n=159)	40 Gy in 4 fractions (n=34)	50 Gy in 4 fractions (n=73)	54 Gy in 3 fractions (n=11)	60 Gy in 8 fractions (n=8)
GTV volume (cm^3)	3.6 (1.2,10.2)	1.8 (0.9,5.0)	3.2 (2.5,5.5)	13.5 (6.2,22.1)	42.0 (34.4,50.1)	45.6 (37.0,62.7)
Maximum dose	130% (126,136)	130% (126,136)	129% (125,135)	130% (125,135)	138% (130,144)	134% (128,141)
PTV D95%	100% (100,100)	100% (100,100)	100% (100,100)	100% (100,100)	100% (99.1,100)	100% (100,100.03)
PTV V90%	100% (99.98,100)	100% (99.99,100)	100% (100,100)	100% (99.97,100)	100% (99.85,100)	100% (99.7,100)
PTV V95%	99.7% (99.4,99.9)	99.7% (99.4,99.9)	99.8% (99.7,99.9)	99.8% (99.4,99.9)	99.3% (98.5,99.8)	99.3% (98.8,99.5)
GTV mean dose	121% (118,126)	122% (118,126)	119% (117,125)	120% (117,125)	120% (118,126)	120% (118,123)
Conformity index	1.04 (1.00,1.11)	1.06 (1.02,1.13)	1.04 (1.02,1.11)	1.02 (1.11,1.06)	0.99 (0.96,1.02)	1.01 (0.99,1.03)

eTable 2. Site of first recurrence, patient level

Group	Whole study cohort (n=217)	Group 1: first primary NSCLC (n=79)	Group 2: new primary or synchronous NSCLC (n=67)	Group 3: lung metastases (n=71)
Local	12 (5.5%)	6 (7.6%)	2 (3.0%)	4 (5.6%)
Regional	18 (8.3%)	10 (12.7%)	7 (10.5%)	1 (1.4%)
Distant	67 (30.9%)	10 (12.7%)	20 (29.9%)	37 (52.1%)
Local and regional	5 (2.3%)	2 (2.5%)	2 (3.0%)	1 (1.4%)
Local & distant	2 (0.9%)	2 (2.5%)	0 (0%)	0 (0%)
Regional & distant	10 (4.6%)	1 (1.3%)	4 (6.0%)	5 (7.0%)
None	103 (47.5%)	48 (60.8%)	32 (47.8%)	23 (32.4%)

eTable 3. Details of cases of equivocal local recurrence reviewed by panel.

Patient group	Num. lesions treated	Possible recurrence time point	Details	Final determination
1	1	4 years	CT suggestive of local recurrence, and new vocal cord paralysis consistent with tumor location	Local recurrence
1	1	15 months	CT and PET with nodular changes and a satellite nodule	Local recurrence
1	1	2.5 years	CT and PET showed serial growth of mass, biopsy showed atypical cells, received reirradiation	Local recurrence
1	1	21 months	Intrapulmonary nodal recurrence outside radiation field	Regional recurrence
1	1	3 years	Nodules appeared around the treated area, but were stable over several scans consistent with post-radiation changes	No recurrence
2	2	7 years	Marginal recurrence, convincing on imaging. Patient received SABR for the recurrence.	Local recurrence
2	2	9 months	CT showed growth of treated tumor PET confirmed and tumor was also hypermetabolic. Patient received SABR for the recurrence	Local recurrence
2	2	2 years	New nodule in lobe far from treated tumor, with concurrent distant recurrence	Distant recurrence
2	1	15 months	New nodule in same lobe far from treated tumor, without other new lesions	New primary
2	2	15 months	Treated tumor was in left lower lobe; developed new nodules along major fissure and adjacent to it in left lower lobe	Distant recurrence

2	1	3 years	New nodule in same lobe with appearance of primary adenocarcinoma. Patient with history of many lung adenocarcinomas.	New primary
2	2	18 months	Recurrence in adrenal gland and multiple out of field nodules in treated lobe	Distant recurrence
2	1	6 months	Recurrence in bone metastasis, hilar node, and multiple out of field nodules in treated lobe and other lobes	Regional and distant recurrence
2	1	18 months	Radiographic changes in same lobe (in and out of field) concerning for aspergillus infection, asymptomatic, awaiting biopsy	No recurrence
3	1	1 year	Innumerable new lung lesions in all lobes	Distant recurrence
3	1	1 year	Widespread new lung lesions in all lobes	Distant recurrence
3	1	6 months	Recurrence in pleural-based lesions including in same lobe	Distant recurrence

eTable 4. Local recurrence by patient group (Kaplan-Meier method)

	1 year	2 years	5 years
Group 1	2.6% (0.7-7.1)	9.6% (4.9-16.2)	16.6% (9.2-25.9)
Group 2	5.2% (2.3-9.9)	7.4% (3.8-12.7)	7.4% (3.8-12.7)
Group 3	3.0% (1.0-6.7)	4.9% (2.2-9.4)	9.3% (4.8-15.6)

90% confidence intervals in parentheses

eTable 5. Local recurrence by patient group, first enrollment per patient only (Kaplan-Meier method). 258 of 285 total tumors were included in this analysis.

	1 year	2 years	5 years
Group 1	3.1% (0.0-6.7)	12.2% (5.1-19.3)	24.1% (11.5-36.7)
Group 2	7.6% (2.2-13.0)	9.7% (3.4-16.0)	9.7% (3.4-16.0)
Group 3	3.7 (0.0-8.0)	8.6% (1.7-15.5)	23.6% (8.6-38.6)

90% confidence intervals in parentheses

eTable 6. Treated tumor recurrence by patient group (cumulative incidence method)

	1 year	2 years	5 years
Group 1	2.6% (0.5-8.2)	7.9% (3.2-15.4)	11.6% (5.2-20.6)
Group 2	4.1% (1.3-9.5)	5.2% (1.9-11.0)	5.2% (1.9-11.0)
Group 3	2.9% (0.8-7.7)	2.9% (0.8-7.7)	5.3% (1.9-11.3)

95% confidence intervals in parentheses

eTable 7. Treated tumor recurrence vs. competing events by tumor size/location. Differences were not statistically significant ($P = 0.21$).

	Tumors	Treated tumor recurrence	Competing event (death or distant recurrence prior to treated tumor recurrence)	Censored
≤10cc peripheral	169	11	94	64
≤10cc central	41	1	21	19
>10 and ≤30cc peripheral	31	5	15	11
>10 and ≤30cc central	25	2	18	5
>30cc peripheral	11	0	9	2
>30cc central	8	1	4	3

eTable 8. Distant recurrence by patient group

	1 year	2 years	5 years
Group 1	10.3% (4.8-18.2)	15.7% (8.6-24.8)	23.2% (13.7-34.3)
Group 2	16.9% (9.0-27.0)	28.7% (18.0-40.3)	53.6% (32.0-71.1)
Group 3	45.7% (33.6-56.9)	54.4% (41.9-65.4)	61.8% (47.1-73.5)

95% confidence intervals in parentheses

eTable 9. Treated tumor recurrence by T stage (primary NSCLC only, so groups 1-2 only).

	1 year	2 years	5 years
T1 (n=145)	3.6% (1.4-7.8)	5.9% (2.8-10.8)	8.2% (5-20.3)
T2 (n=37)	2.7% (0.2-12.3)	8.1% (3.2-38.5)	8.1% (3.2-38.5)

95% confidence intervals in parentheses

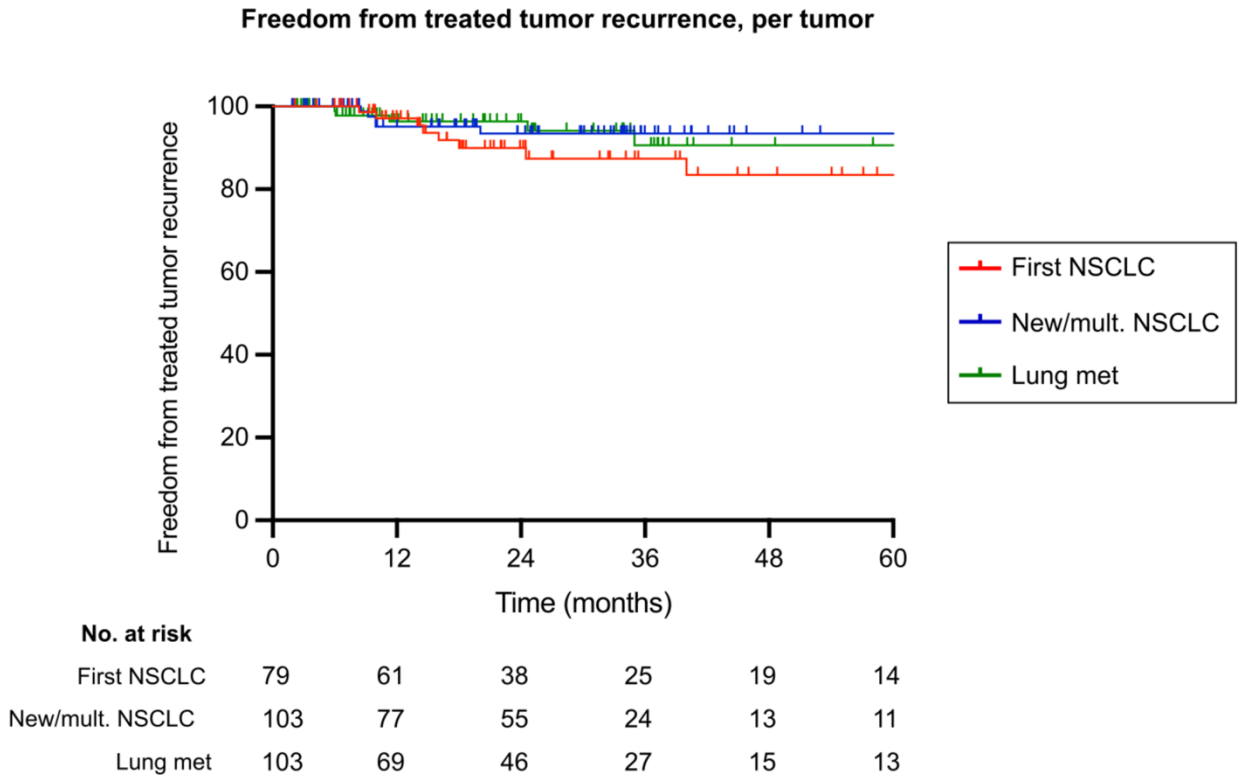
eTable 10. Treated tumor recurrence by histology (primary NSCLC only, so groups 1-2 only).

	1 year	2 years	5 years
Adenocarcinoma (n=105)	2.7% (0.7-7.0)	6.3% (2.8-11.8)	6.3% (2.8-11.8)
Squamous cell carcinoma (n=28)	9.7% (2.4-23.2)	12.9% (4.0-27.3)	23.3% (8.2-42.8)
Other/unknown (n=28)	0% (0-0)	0% (0-0)	0% (0-0)

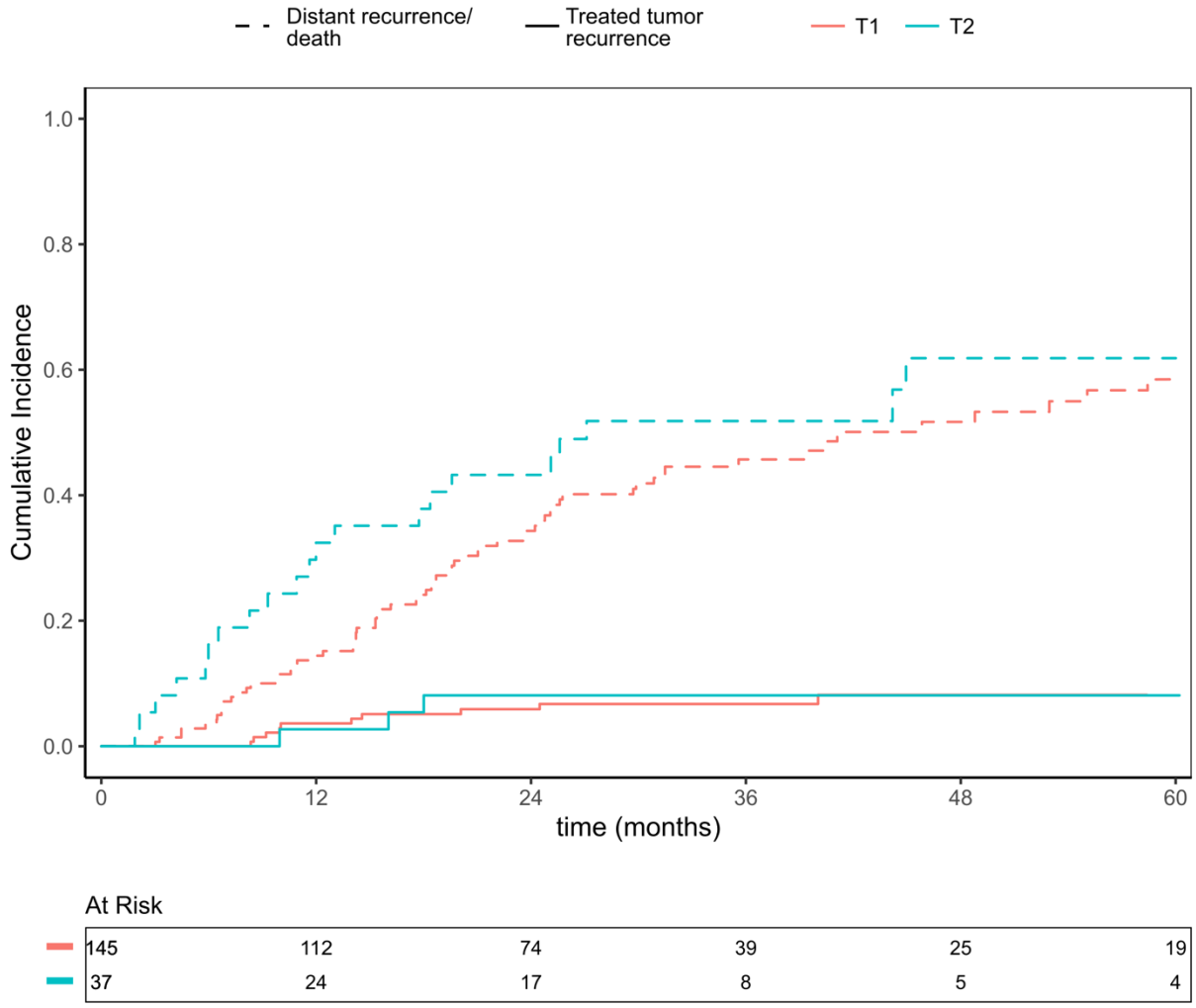
95% confidence intervals in parentheses

Supplementary Figures

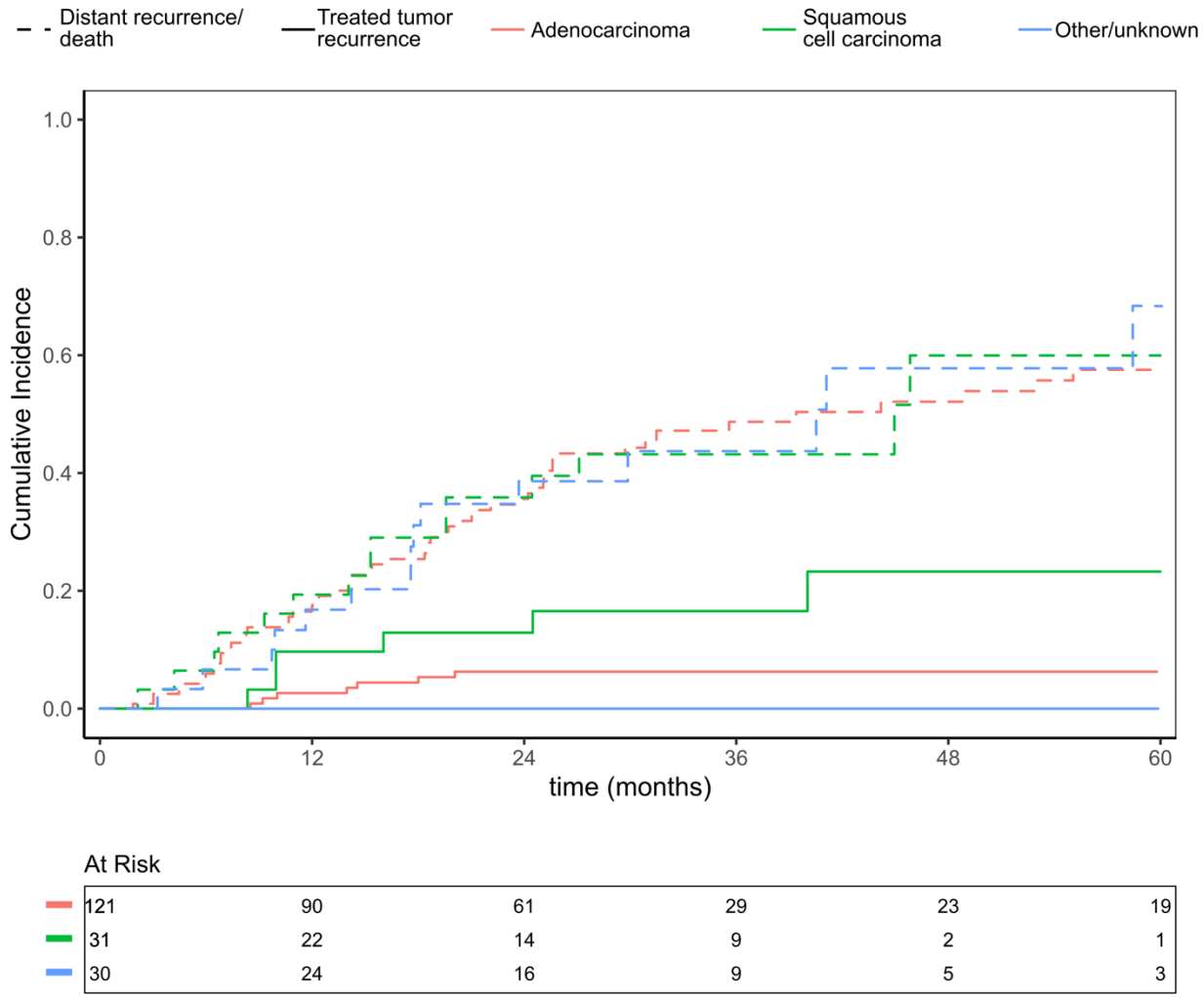
eFigure 1. Treated tumor recurrence, per tumor, Kaplan-Meier plot. Censored at time of death, distant recurrence, or loss to follow-up. This figure allows comparison of our results to other studies that used Kaplan-Meier method instead of competing risks approach. First NSCLC (group 1), New/multiple NSCLC (group 2), Lung metastases (group 3)



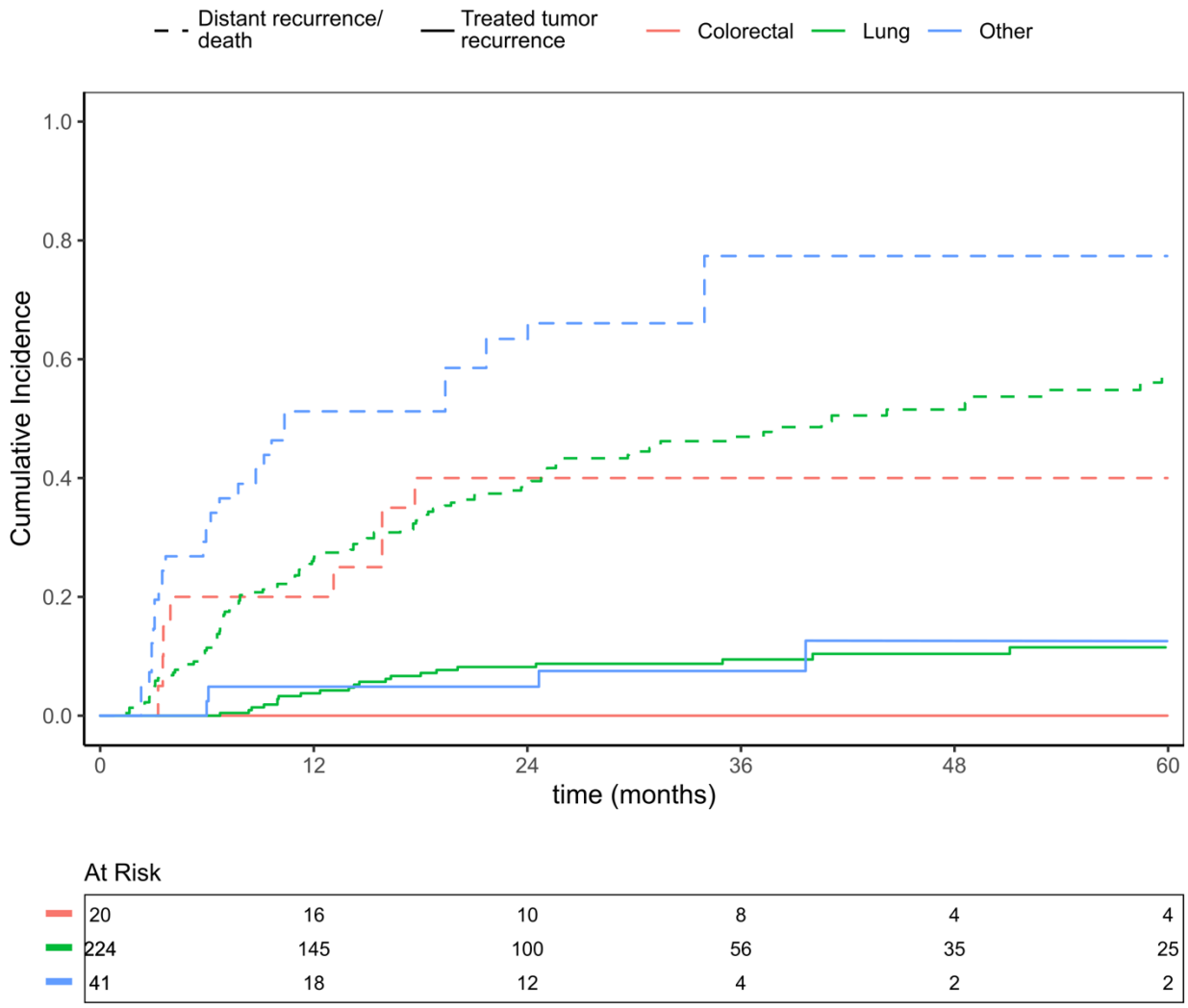
eFigure 2. Treated tumor recurrence by T stage, per tumor (primary NSCLC only, so groups 1-2 only). Competing events are distant recurrence or death. Treated tumor recurrence was similar between T1 and T2 (P = 0.52).



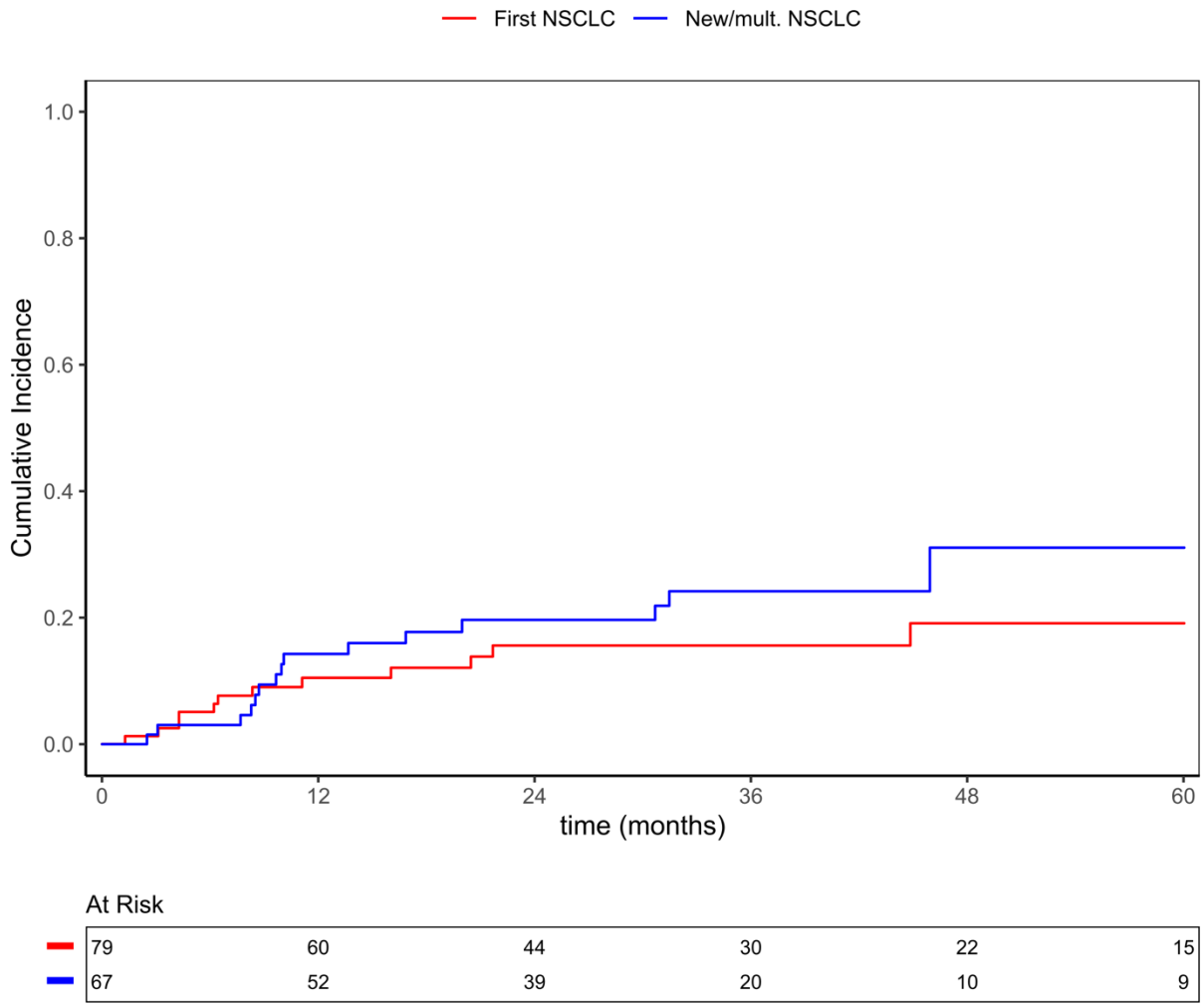
eFigure 3. Treated tumor recurrence by histology, per tumor (primary NSCLC only, so groups 1-2 only). Competing events are distant recurrence or death. Treated tumor recurrence was greater in SCC (P = 0.03).



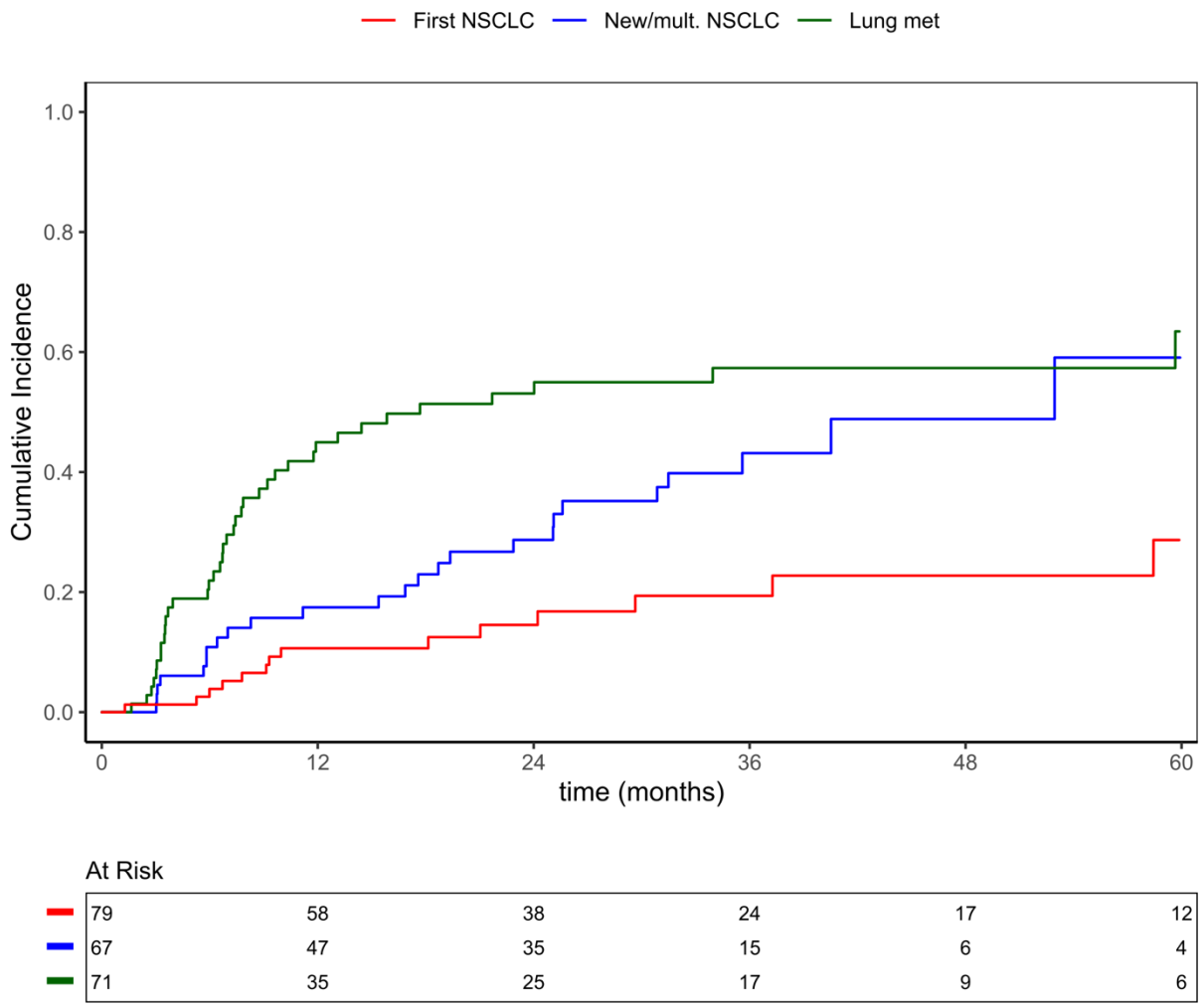
eFigure 4. Treated tumor recurrence by primary tumor site, per tumor (all patients). Competing events are distant recurrence or death.



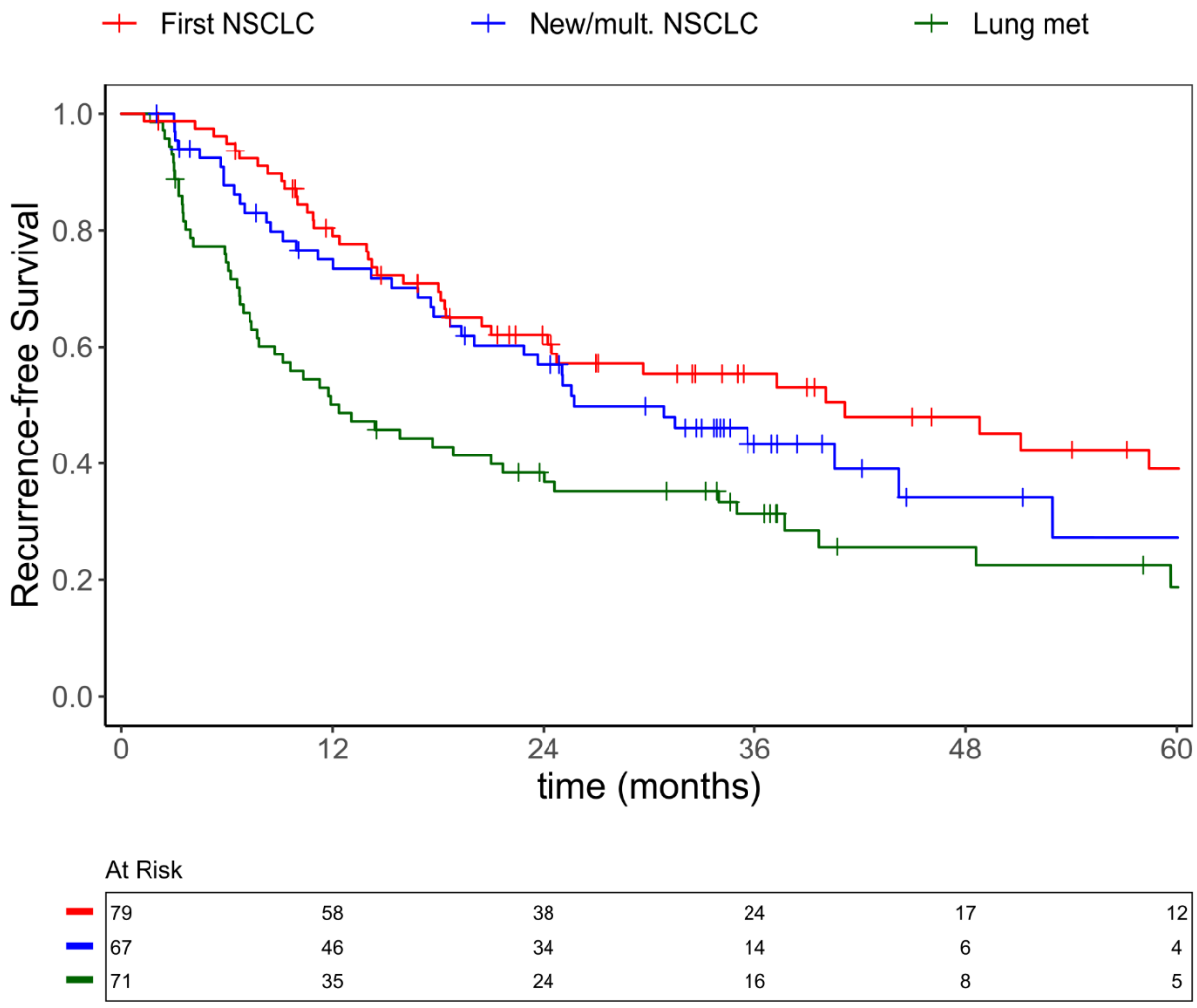
eFigure 5. Cumulative incidence of regional recurrence, per patient (Primary NSCLC Only, so Groups 1-2 Only). First NSCLC (group 1), New/multiple NSCLC (group 2)



eFigure 6. Cumulative incidence of distant recurrence, per patient. First NSCLC (group 1), New/multiple NSCLC (group 2), Lung metastases (group 3)



eFigure 7. Recurrence-free survival, per patient. First NSCLC (group 1), New/multiple NSCLC (group 2), Lung metastases (group 3)



eFigure 8. Patient with large ultra-central tumor and possibly treatment related grade 5 toxicity. Dose was 60 Gy in 8 fractions. Maximum dose to the proximal bronchial tree was 67.9 Gy. GTV=gross tumor volume (red contour). IDL=isodose line (orange, green, cyan contours).