

Peer review file

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Reviewer A

Comment: This is a well-conceived study that meaningfully adds to the existing body of literature. It deals well with the inherent limitations of such a small sample size. The salient issues of this unique clinical circumstance are appropriately covered. Nonetheless, there are significant problems with grammar and syntax that will need to be revised prior to publication.

Reply:

Thank you for the positive feedback and valuable recommendation. The manuscript has been carefully revised and checked by a professional editor before resubmission. The certificate is shown below.



Reviewer B

Comment 1: Line 11: The study is described as an “observational longitudinal cohort study”. This reviewer feels that something along the lines of “a retrospective, pooled analysis” would more clearly communicate the design of the study.

Reply 1: We thank the Reviewer for your suggestion and agree that this should be corrected. As such, we described the study as “a retrospective, pooled analysis” in the article.

Changes in the text: In the abstract, the original sentence “*This is an observational longitudinal cohort study*” was replaced by “*This is a retrospective, pooled analysis*” (see Page3, Line23)

Comment 2: Lines 23–24: It is mentioned that “fetal complications were observed in babies whose mothers were treated during pregnancy”. Please quantify (if possible) the frequency of fetal complications among newborns whose mothers received antineoplastic treatment during pregnancy.

Reply 2: Thanks for your valuable suggestion. We guessed that it would be better to response Comment 2, Comment 11 and Comment 15 together here. The three comments recommended us to mention the frequency of fetal complications in different population in the results section.

Comment 11 and Comment 15 are as follows:

Comment 11: Lines 149–150: Please quantify the overall frequency of fetal adverse effects in babies whose mothers received antineoplastic treatment.

Comment 15: Lines 207–208: How often were fetal adverse events reported in babies whose mothers were not treated during pregnancy? I think this is important and therefore ask you to mention this in the results section.

We have carefully reviewed the raw data, and compared the number of patients under each condition in the following table:

Comment	Antineoplastic treatment	Total cases	Cases reported fetal health condition	Cases observed Fetal complications	Frequency
Comment 2	Treated during pregnancy	24	21	8	38%
Comment 15	Untreated during pregnancy	48	25	13	52%
Comment 11	Treated during pregnancy or after delivery	64	38	19	50%

Since the fetal complications was not associated with antineoplastic treatment after delivery, we launched a Chi-Square Test between patients treated and untreated during pregnancy. No significant difference was observed in the frequency of fetal complications (38% v.s 52%, $P=0.346$). We have added the fetal complications frequency under various conditions in the results section. Chi-Square Test has been included in the methods section, and statistical result has been added in the results section.

Changes in the text:

a. In the methods section, the Chi-Square Test has been included, stating that “*Chi-Square Test*

was launched to compare the frequency of fetal complications between patients treated and untreated during pregnancy". (see Page7, Line86-87)

- b. In the results section, we have added the frequency of fetal complications in different population and statistical result, which states as "***Fetal adverse effects were observed in babies whose mothers received anticancer therapies during pregnancy (Table 3). The frequency was about 38%.....The frequency of fetal adverse events in babies whose mothers did not receive antineoplastic treatment during pregnancy was 52%. No significant difference was observed in the frequency of fetal complication between patients treated and untreated during pregnancy (38% v.s 52%, P=0.346). The overall frequency of fetal adverse effects in babies whose mothers received antineoplastic treatment was 50%***". (see Page10-11, Line131-138)

Comment 3: Lines 33–34: I might have missed it — and if so, I apologize — but apparently the definition of pregnancy-associated lung cancer used in the introduction is not mentioned in the corresponding reference (Boussois S. et al). Where does the definition come from?

Reply 3: Thank you for pointing this out. We have changed the original reference into the correct reference. (Zagouri F et al. 2016. Cancer in pregnancy: disentangling treatment modalities. ESMO Open. 1: e000016. DOI: 10.1136/esmoopen-2015-000016)

Changes in the text: In the introduction section, the paper was referred in the sentence "***Pregnancy-associated lung cancer is defined as lung cancer diagnosed during pregnancy and within one year of delivery***". (see Page4, Line40).

Comment 4: Lines 42–44: You reference a single-center study from the US (reference 3).

a. To improve readability, please mention that the eight patients were diagnosed during pregnancy or the postpartum period.

b. You simply state that eight patients had ALK-rearrangement or EGFR mutations. It would be more informative to state that all patients (n = 8) diagnosed with lung cancer during pregnancy or the postpartum period were ALK- or EGFR-positive.

Reply 4: Thanks for your valuable suggestions. To clarify the study clearly, the relevant details have been added. Firstly, we mentioned that eight patients were diagnosed during pregnancy or the postpartum period in the US research center. Then we stated that six of them were ALK positive and two patients were EGFR positive.

Changes in the text: In the introduction section, the original statement has been revised to indicate the total patients diagnosed and their genotypes, and now states "***A single-center study from the United States reported that eight patients were diagnosed with lung adenocarcinoma during pregnancy or in postpartum period. Six of them had anaplastic lymphoma kinase (ALK) gene rearrangement and the other two carried epidermal growth factor receptor (EGFR) mutation***". (see Page4-5, Line47-49)

Comment 5: In the methods section, please state which staging system(s) (e.g. UICC/AJCC) and version(s) were used.

Reply 5: We thanks for the Reviewer for your request. Most of the patients were diagnosed from 2009 to 2017, and staged by the 7th Edition of TNM Staging Criteria (UICC). We have added it to the methods.

Changes in the text: As suggested, we had added the staging system and version in the methods section as "***Most of the patients were staged by the 7th Edition of TNM Staging Criteria (UICC)***". (see Page6, Line75-76)

Comment 6: Lines 90–91: In the methods section, you mention that “the safety of profile during pregnancy was reviewed”. I think I understand, but the sentence is confusing — consider revising.

Reply 6: Thanks for your valuable advice. According to your suggestion, we changed the confusing phrase “the safety of profile” to “the safety profile”.

Changes in the text: In the abstract and methods section, the original sentence “*The safety of profile during pregnancy was also evaluated*” was replaced by “*The safety profile during pregnancy was also evaluated*”. (see Page2, Line25 and Page7, Line86).

Comment 7: In the methods section on statistics, you do not mention the use of Cox Regression analysis to estimate survival differences. However, given that you report several hazard ratios, I would wager that you have used this analysis (?). If correct, it should be stated, and how/if you assessed the proportional hazards assumption.

Reply 7: Thanks for your careful review. We used the Kaplan-Meier method to construct survival curves and calculate median OS. Cox Regression analysis was used to derive hazard ratios and 95% confidence intervals. We have added it to the methods section on statistics.

Changes in the text: As your suggestion, the methods section on statistics has been restructured as “*Statistical analysis was performed using GraphPad Prism 7.0 and SPSS 20.0. Clinicopathological characteristics and patient outcomes were summarized descriptively. The Kaplan-Meier method was used to construct survival curves and calculate median OS. Cox Regression analysis was used to derive hazard ratios and 95% confidence intervals. The complications observed in fetus whose mothers received antineoplastic treatment during pregnancy were reviewed. Chi-Square Test was launched to compare the frequency of fetal complications between patients treated and untreated during pregnancy. A P value ≤ 0.05 was considered statistically significant*”. (see Page7, Line84-88)

Comment 8: In the results section, consider mentioning how many patients were diagnosed during pregnancy vs after delivery. How many of the four patients who gave birth to live babies were diagnosed during pregnancy?

Reply 8: Thanks for your valuable recommendations. In our research center, three patients were diagnosed during pregnancy and eight patients were diagnosed after delivery. Of the four patients who gave birth to live babies, none of them were diagnosed during pregnancy. Overall, 55 patients were diagnosed during pregnancy and 16 patients were diagnosed after delivery. We have added the number of cases diagnosed during pregnancy or after delivery respectively in the results section, and listed the data in Table1 and Table2.

Changes in the text:

- a. In the results section “Summaries of the Cases in Guangdong Lung Cancer Institute”, the original sentence “*Most patients were diagnosed during pregnancy and within three months of delivery*” was replaced by “*Three patients were diagnosed during pregnancy and eight patients were diagnosed after delivery*”. (see Page8, Line97-98) In the results section “Total Cases of Gestational Lung Cancers in Literature”, the original sentence “*Most cases were diagnosed in the second or the third trimester*” was replaced by “*55 patients were diagnosed during pregnancy and 16 patients were diagnosed after delivery*”. (see Page9, Line109-110)
- b. The diagnosis time of each patient in our research center was listed in Column7 “Gestational age at diagnosis” of Table1. The total number of patients diagnosed in different periods was listed in Line “Time of diagnosis” of Table2. Table1 & Table2 are shown below.

Table 1: Clinicopathologic features and outcome of patients with pregnancy-associated NSCLC in Guangdong Lung Cancer Institute.

Case	Age at diagnosis (years)	Performance status	Smoking History	Symptoms	Time interval from symptom onset to hospital (months)	Gestational age at diagnosis	Pathology	Stage	Molecular driver	Fetal outcome	Treatment during pregnancy	Treatment after delivery		Survival outcome (months, since diagnosis)
												First line	Other therapies	
1	25	1	No	Cough, dyspnea	1	During pregnancy	Adenocarcinoma	IV	ALK	Induced abortion	No	Crizotinib, PFS=18.4m	Brain IMRT	36 months, Alive
2	28	1	No	Shoulder pain	1	1 week postpartum	Adenocarcinoma	IV	ALK	Induced abortion	No	NA	NA	16 months, Dead
3	28	1	No	Cough, fever	1	1 month postpartum	Adenocarcinoma	IV	ALK	NA	No	Crizotinib	Carboplatin + pemetrexed + bevacizumab; lorlatinib, PFS=9.5m; albumin-bound paclitaxel	38 months, Alive
4	37	1	No	Cough, dyspnea	2	1 week postpartum	Adenocarcinoma	IV	ALK	Live birth	No	Ensartinib, PFS=13m	NA	21 months, Alive
5	31	2	No	Lumbago, dyspnea	0.5	16 weeks	Adenocarcinoma	IV	EGFR 19del	Induced abortion	No	Icotinib	NA	17 months, Dead
6	35	1	No	Physical examination	NA	1 weeks postpartum	Adenocarcinoma	I	Wild-type	Spontaneous abortion	No	VATS right lobectomy with mediastinal lymph node dissection	NA	8 months, Alive
7	33	3	No	Cough, dyspnea, leg pain	3	1 month postpartum	Adenocarcinoma	IV	Wild-type	Live birth	No	Carboplatin + gemcitabin	NA	10 months, Dead

8	29	3	No	Leg edema, Lumbago	1.5	3 months postpartum	Lymphoepithelioma-like carcinoma	IV	Wild-type	Live birth	No	erlotinib	Afatinib, bevacizumab	2.6 months, Dead
9	42	1	No	Chest pain	12	12 months postpartum	Lymphoepithelioma-like carcinoma	IV	Wild-type	Live birth	No	Carboplatin + pemetrexed + bevacizumab, PFS=12m	Nivolumab	15 months, Alive
10	28	NA	No	Cough, headache	6	16 weeks	Adenocarcinoma	IV	Wild-type	Intrauterine fetal demise	No	NA	NA	0.33 months, Dead
11	36	0	No	Physical examination	NA	1 week postpartum	Lymphoepithelioma-like carcinoma	NA	NA	Induced abortion	No	Left lobectomy with mediastinal lymph node dissection	NA	19 months, Alive

Table 2: Characteristic and outcome of 77 patients with NSCLC associated with pregnancy

Characteristic/outcome	Guangdong Lung cancer	Literature Reports	Total
	Institute (n=11)	(n=66)	(n=77)
Age (yr)			
Median	31	34	34
Range	25–42	24–43	24–43
Time interval from symptom onset to hospital (m)			
Median	1.5	2	2
Range	0.5–12	0.1–24	0.1–24
Time of diagnosis			
The first trimester of gestation	0	8	8
The second trimester of gestation	2	30	32
The third trimester of gestation	0	15	15
Postpartum period	7	9	16
After death	0	2	2
NA	2	2	4
Smoking history			
Yes	0	16	16
No	11	29	40
NA	0	21	21
Symptoms			
Cough	4	30	34
Dyspnea	4	27	31
Chest/back pain	3	13	16
Hemoptysis	0	6	6
Fever	1	7	8
Weight loss	0	6	6
Stage			
I-II	1	2	3
III-IV	9	62	71
NA	1	2	3
Pathology			
Adenocarcinoma	8	44	52

Squamous cell carcinoma	0	6	6
Others	3	15	18
NA	0	1	1
Genotype			
EGFR	1	10	11
ALK	4	12	16
Wild type	5	2	7
NA	1	42	43
Fetal outcome			
Normal	0	30	30
Induced abortion	4	11	15
Spontaneous abortion	1	1	2
NA	6	20	26
Treatment during pregnancy			
Yes	0	24	24
No	10	38	48
NA	1	3	4
Treatment after delivery			
Yes	9	45	54
No	0	16	16
NA	2	5	7
Therapy methods			
Surgery	2	9	11
Chemotherapy	3	30	33
Radiotherapy	0	22	22
Targeted therapy	5	25	30
Immunotherapy	1	0	1

NA: not available; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor

Comment 9: Line 130: Please change “people” to “patients”. Moreover, “some” is not very informative, consider changing to a number or proportion (or an approximation thereof).

Reply 9: Thanks for your valuable advice. We have changed “people” to “patients”, “some” to a number.

Changes in the text: In the results section, we have replaced the sentence “*some people received surgery and radiotherapy*” by “*11 patients received surgery and 22 patients received radiotherapy*”. (see Page9, Line117)

Comment 10: Line 144: You state that there were 13 patients with EGFR mutations, but in Table 2 and in the previous section (ll. 125–126) it is stated that there were 11 patients with EGFR. Which is it?

Reply 10: Thanks for your careful review. We have carefully checked this again. There were 11 patients with EGFR mutations totally. But only 10 patients with follow-up data were included in the survival analysis. We have corrected the phrase “EGFR (n = 13)” to “EGFR (n = 10)”.

Changes in the text: In the results section, we have deleted the original statement “*Patients with ALK (n = 13) and EGFR (n = 13) mutations exhibited significantly higher OS than those with the wild-type (n = 7)*”, which now states “*Patients with ALK (n = 13) and EGFR (n = 10) mutations exhibited significantly better OS than those with the wild-type (n = 7)*”. (see Page10, Line127-128)

Comment 11: Lines 149–150: Please quantify the overall frequency of fetal adverse effects in babies whose mothers received antineoplastic treatment.

Reply 11: Thanks for your suggestion. We have replied it in Comment 2.

Changes in the text: We have made some revisions. Please refer to Comment 2.

Comment 12: Lines 163–164: “Initiation of anticancer therapies during pregnancy did not improve the OS”. This is one of the main conclusions of the study, (to my understanding) based on the finding that patients treated during pregnancy did not have longer OS than patients treated after delivery. I have a few questions regarding this interpretation:

a. How many of the patients treated after delivery were diagnosed during pregnancy? If a large proportion of those treated after delivery were also diagnosed after delivery, the analysis may be unfit to assess whether patients diagnosed during pregnancy should have their treatment delayed or not.

b. How many of the patients treated during pregnancy and after delivery were EGFR- or ALK-positive, respectively? This could be a possible confounder, given the large survival differences across these subgroups (Figure 3).

I believe these considerations should at least be acknowledged as possible limitations regarding the interpretation of the effect of antineoplastic treatment during pregnancy.

Reply 12: We thank the Reviewer for your questions and agree that the conclusion should be revised. The original conclusion was not rigorous, which might mislead the readers. Therefore, we have revised the conclusion as “No significant difference in the OS was observed between patients treated during pregnancy and patients treated after delivery”. Besides, the sample size of study was small and the baseline characteristics were unbalanced across the two treatment groups. We have also listed these considerations in the limitations of our study.

Changes in the text:

a. In the abstract, we have deleted the original conclusion “*Initiation of anticancer therapies after delivery was recommended because initiation during pregnancy did not improve the OS*”, and revised the conclusion as “*No significant difference in the OS was observed*”.

between patients treated during pregnancy and patients treated after delivery". (see Page4, Line34-36)

- b. In the discussions section, we have deleted the original similar conclusions "*Initiation of anticancer therapies during pregnancy did not improve the OS. Therefore, we recommend the initiation of intervention after delivery*". (see Page11, Line144-146; Page 12, Line163-164 and Page14, Line192-193) Instead, the statements have been replaced by "*No significant difference in the OS was observed between patients treated during pregnancy and patients treated after delivery*". (see Page11, Line144-145 and Page12, Line163) Besides, we have included the above considerations in the limitations, stating as "*The sample size of study was small and the baseline characteristics were unbalanced across the groups.....Therefore, the conclusions should be interpreted carefully*". (see Page14, Line186-188)

Comment 13: Line 177: Change "concurrent with" to "consistent with".

Reply 13: Thanks for your valuable suggestion. We have changed the phrase "concurrent with" to "consistent with".

Changes in the text: In the discussions section, the original sentence "*This finding was concurrent with a previous report by Dagogo-Jack et al*" was replaced by "*This finding was consistent with a previous report by Dagogo-Jack et al*". (see Page12, Line154)

Comment 14: Lines 202–205: Consider adding that the concentration of crizotinib in umbilical cord blood has been shown to be extremely low (Jensen K et al. Antineoplastic treatment with crizotinib during pregnancy: a case report. Acta Oncologica 2018. <https://doi.org/10.1080/0284186X.2018.1497302>).

Reply 14: Thanks for your valuable suggestion. The article enriched our manuscript and increased the readability. We have added the reference in the discussions section.

Changes in the text: In the discussions section, we referred the article in the sentence "*The concentration of crizotinib in umbilical cord blood was shown to be extremely low in a case report (16)*". (see Page13, Line173-174)

Comment 15: Lines 207–208: How often were fetal adverse events reported in babies whose mothers were not treated during pregnancy? I think this is important and therefore ask you to mention this in the results section.

Reply 15: Thanks for your suggestion. We have replied it in Comment 2.

Changes in the text: We have made some revisions. Please refer to Comment 2.

Comment 16: Lines 221–223: I believe it should also be mentioned that all cases were evaluated retrospectively (both patients from your centre and from the literature), resulting in a considerable proportion of missing data, especially on genotyping and fetal outcomes.

Reply 16: Thanks for your valuable advice. We acknowledged that a proportion of data was missed in this retrospective study. We have added these limitations in the discussions section.

Changes in the text: In the discussions section, we have included it in the limitations, stating as "*All cases were evaluated retrospectively, resulting in a considerable proportion of missing data*". (see Page14, Line186)

Comment 17: Figure 1: Nicely shows the case selection process.

Reply 17: We are grateful for your positive and encouraging comment.

Changes in the text: N/A

Comment 18: Figure 2: Consider adding a risk table below the diagram.

Reply 18: Thanks for your constructive suggestion. To improve the readability, we have provided a risk table below the diagram and restructured the Figure2.

Changes in the text: The revised Figure2 is shown below and will be sent back to you as an additional file.

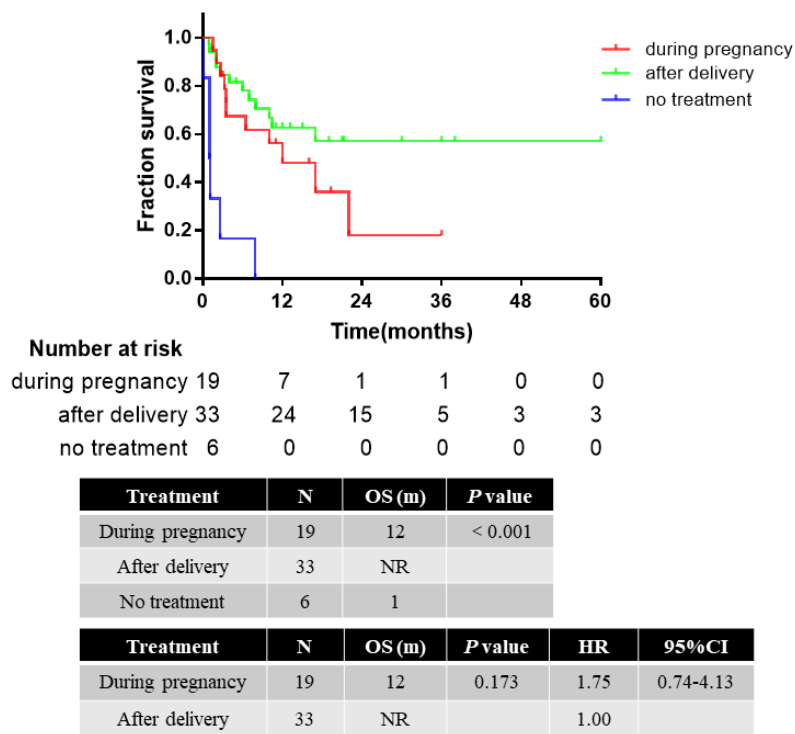


Figure 2. OS of patients initiated anticancer treatment during pregnancy, after delivery, no treatment. (1) treated during pregnancy vs. treated after delivery vs. no treatment (12 months vs. NR vs. 1 months; $P < 0.001$). (2) treated during pregnancy vs. treated after delivery (12 months vs. NR; $P = 0.173$; $HR = 1.75$, 95%CI 0.74 to 4.13)

Comment 19: Figure 3: Consider adding a risk table below the diagram.

Reply 19: Thanks for your constructive suggestion. To improve the readability, we have provided a risk table below the diagram and restructured the Figure3.

Changes in the text: The revised Figure3 is shown below and will be sent back to you as an additional file.

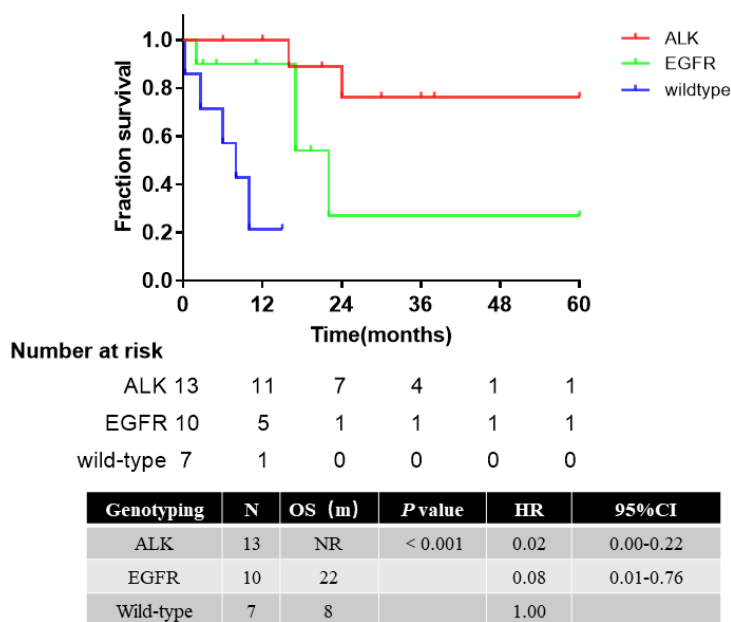


Figure 3. OS of patients with EGFR mutation, ALK mutation and wild-type.

Comment 20: Tables 1 & 2 are fine, and I have no comments in this regard.

Reply 20: We appreciate your encouraging feedback. But we found a mistake in Table2. There were 24 patients, not 25, who received antineoplastic therapy during pregnancy. We have revised it in Table2.

Changes in the text: The number was shown in Line “Treatment during pregnancy” of Table2. Please refer to the revised Table 2 in Comment 8. The revised table2 will be sent back to you as an additional file.

Comment 21: Table 3: Nice and comprehensive. You could consider ordering the patient cases according to one of the variables, e.g. pathology or treatment during pregnancy, but this is a minor thing.

Reply 21: Thanks for your valuable suggestion. We have arranged the patient cases by pathology.

Changes in the text: The revised Table 3 is shown below and will be sent back to you as an additional file.

Table 3: Adverse effects of fetus in patients treated during pregnancy.

Reference	Age	Pathology	Stage	Genotype	Gestational age at diagnosis (wk)	Treatment during pregnancy	Timing of delivery (wk)	Fetal outcome	Maternal outcome (months, since diagnosis)
Boussios et al. (1)	35	Adenocarcinoma	UK	UK	6	Cisplatin + vinorelbine	33	UK	6.50, Dead
Garrido et al. (21)	34	Adenocarcinoma	III	UK	27	Cisplatin + vinorelbine	39	Normal	16.00, Alive
Pa et al. (22)	31	Adenocarcinoma	IV	UK	26	Cisplatin + vinorelbine	26	Normal	UK
Boussios et al. (1)	31	Adenocarcinoma	IV	UK	20	Cisplatin + vinorelbine	26	Respiratory distress, Necrotizing enteritis	2.07, Dead
Garcia-Gonzalez et al. (25)	39	Adenocarcinoma	III-IV	UK	17	Cisplatin + paclitaxel	30	Respiratory distress	10.00, Dead
Iliaz et al. (26)	28	Adenocarcinoma	IV	UK	22	Cisplatin	32	Normal	UK
Kim et al. (27)	35	Adenocarcinoma	IV	UK	31	Cisplatin + docetaxel	33	Normal	10.00, Alive
Dagogo-Jack et al. (3)	29	Adenocarcinoma	IV	ALK	9	Carboplatin + paclitaxel, Gamma knife radiosurgery	34	Normal	36.00, Alive
Boussios et al. (1)	42	Adenocarcinoma	IV	UK	13	Carboplatin + paclitaxel	27	Normal	3.53, Dead
Azim et al. (29)	33	Adenocarcinoma	IV	UK	19	Carboplatin + paclitaxel	30	Normal	3.50, Dead
Holzmann et al. (30)	29	Adenocarcinoma	IV	EGFR 19del	26	Carboplatin + docetaxel, Palliative radiotherapy for the thoracic spine	31	Normal	17.00, Dead
Gil et al. (31)	33	Adenocarcinoma	IV	EGFR 19del	26	Gefitinib, Stereotactic radiotherapy for brain	35	Normal	22.00, Dead
Lee et al. (32)	38	Adenocarcinoma	IV	EGFR 19del	26	Gefitinib	36	Normal	3.00, Alive
Ji et al. (14)	40	Adenocarcinoma	IV	EGFR 19del	10	Erlotinib, Radiotherapy for brain	37	Intrauterine growth restriction	19.30, Alive
Rivas et al. (13)	40	Adenocarcinoma	IV	EGFR 21L858R	3	Erlotinib	33	Intrauterine growth restriction, Oligohydramnios	11.00, Alive
Padrao et al. (33)	36	Adenocarcinoma	IV	ALK	22	Crizotinib	30	Placental metastasis	UK
Mujaibel et al. (10)	35	Adenocarcinoma	IV	UK	31	Whole-brain radiotherapy	34	Normal	2.70, Dead
Magne et al. (34)	38	Adenocarcinoma	IV	UK	24	Intracranial tumor resection, Whole-brain radiotherapy	UK	Normal	58.00, Alive
Wang et al. (23)	27	Squamous cell carcinoma	IV	UK	1	Cisplatin + vinorelbine	37	Low birth weight	9.00, Dead
Yates et al. (24)	26	Lymphoepithelioma-like carcinoma	III	UK	18	Cisplatin + docetaxel	35	Normal	16.00, Alive
Kim et al. (7)	38	Large cell carcinoma	II	UK	24	VATS right lobectomy with mediastinal lymph node	37	Normal	10.00, Alive

Boussios et al. (1)	32	large cell carcinoma	IV	UK	19	dissection			
Gurumurthy et al. (28)	38	Poorly differentiated carcinoma	IV	UK	24	Cisplatin + etoposide	33	Normal	3.27, Dead
Boussios et al. (1)	26	Poorly differentiated carcinoma	IV	UK	17	Carboplatin + gemcitabine	28 ⁺	Anemia, Chronic lung diseases	1.53, Dead
						Cisplatin + vinorelbine, Gamma knife radiosurgery	23	Oligohydramnios	12.00, Dead
