Journal Pre-proof

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PII: S1525-7304(22)00255-8
DOI: https://doi.org/10.1016/j.cllc.2022.11.003
Reference: CLLC 1549

To appear in: *Clinical Lung Cancer*

Received date: Jul 27, 2022
Revised date: Oct 28, 2022
Accepted date: Nov 4, 2022

Please cite this article as: Emily A. Simons MD, MPH , Tejas Patil MD , D. Ross Camidge MD, PhD , Pregnancy and pathways to motherhood in oncogene-driven lung cancer: A single institution experience, *Clinical Lung Cancer* (2022), doi: https://doi.org/10.1016/j.cllc.2022.11.003

Pregnancy and pathways to motherhood in oncogene-driven lung cancer: A single institution experience

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Funding
The work of DRC was partially supported by the University of Colorado Cancer Center's Thoracic Oncology Research Initiative and the Joyce Zeff Chair in Lung Cancer Research. The work of TP was partially supported by EMD Soreno and Janssen.

Conflicts of interest
Dr. Simons has nothing to disclose.
Dr. Camidge reports honoraria from Roche/Genentech and Takeda Clinical Trials (institutional) sponsored by Pfizer, Roche/Genentech and Takeda.
Dr. Patil reports honoraria from or advisory roles with Astrazeneca, Biocept, Bristol-Myers Squibb, Caris, Guardant Health, Guidepoint, EMD Soreno, Janssen, Mirati Therapeutics, Natera, Pfizer, Sanofi, Roche/Genentech, Takeda and Elevation Oncology (Data Safety Monitoring Board.)

Credit author statement

Emily A. Simons: Methodology, Data Curation, Formal analysis, Visualization, Writing - Original Draft

Tejas Patil: Resources, Data Curation, Writing - Review & Editing

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Word Count: 2050 exclusive of abstract and microabstract

MicroAbstract

Women of reproductive potential diagnosed with metastatic oncogene-driven lung cancer often desired children prior to their diagnosis and have the possibility of many years of response to targeted therapy. We share our experience with pregnancy, surrogacy, and adoption in patients with lung cancer. Four women were diagnosed with lung cancer during pregnancy, all of whom had an ALK fusion. Three women had a desired pregnancy terminated prior to or during treatment with an ALK inhibitor due to insufficient drug safety information. Six women with metastatic oncogene driver lung cancer attempted to have a child after diagnosis, of which three were successful via gestational surrogate or adoption.

Abstract

Introduction: Oncogene-driven non-small cell lung cancer (NSCLC) disproportionately affects women of reproductive age. With increasing survival, new challenges are arising at the intersection of targeted cancer treatment and motherhood. We share our institution's experience with pregnancies and other pathways to motherhood in women with oncogene-driven lung cancer.

Methods: We reviewed cases of NSCLC in women ages 18-44 at time of cancer diagnosis (all stages) who received cancer care within our institutional network. We describe the incidence, features and outcomes related to pregnancy, surrogacy, adoption and patient survival.

Results: Fifty of 55 (91%) women aged 18-44 with NSCLC had an identified oncogene driver. Oncogene-driven lung cancer was diagnosed within a year of pregnancy in 17% of cases. Women with ALK driven lung cancer tended to be younger by an average of 3.9 years compared to other NSCLC and were more likely to be nulliparous at diagnosis in part due to age. Three patients, either pregnant at diagnosis or who became pregnant while on therapy, elected to undergo a termination. Six patients pursued motherhood after diagnosis via adoption and or gestational surrogacy.

Conclusion: Pregnancy is not an uncommon occurrence around the time of an ALK or EGFR driven lung cancer diagnosis, likely due to young age at time of diagnosis relative to NSCLC with no known oncogene drivers. Gestational surrogacy and adoption are already feasible pathways to motherhood. Terminations have occurred for those on therapy at the time. Detailed studies of the safety of different targeted therapies in pregnancy are desperately needed.

Keywords: gestational surrogate, adoption, non-small cell lung cancer, molecular driver, targeted therapy

Introduction

Non-small cell lung cancer (NSCLC) driven by several oncogenes, including EGFR, ALK, and ROS1, disproportionately affects women of reproductive potential relative to other forms of NSCLC[1,2]. In an era when many years of disease control with oncogene-targeted therapy may be possible, a new clinical challenge of managing the events and expectations of motherhood in such patients is emerging.

Up to one third of NSCLC may be driven by an acquired alteration in an oncogene for which a targeted therapy exists. Many of these alterations tend to be enriched in younger patients, in females, in those with non-squamous NSCLC, in those without a significant smoking history and in certain racial groups, with the exact demographic and clinical factors varying by oncogene[3,4]. A subset of patients on targeted therapy for oncogene driven-lung cancer experience prolonged clinical benefit from therapy and the maximum duration of benefit to many new targeted therapies in lung cancer is currently unknown. About 10-15% of women with lung cancer are of reproductive age at the time of their initial diagnosis.[1] In two cases series of lung cancer diagnosed in the peripartum period, EGFR mutant or ALK rearranged lung cancers combined accounted for 8/8 and 5/11 cases, bringing into question whether there is an increased incidence of lung cancer diagnosis in the peri-pregnancy period in women with EGFR or ALK alterations compared to other oncogene derangements[5,6]. However, this association could be mostly explained by age and should not be interpreted as causation. Unlike EGFR or smoking-related lung cancer, ALK alterations appear to occur with equal frequency across the adult age spectrum[7]. While the median age of patients with EGFR alterations is older than patients with ALK fusions, this remains the most common oncogene driver in lung cancer generally and thus still common among younger patients.[8]

Patients from around the world have contacted our institution, which is a referral center for lung cancer, for advice on management of targeted therapies in relation to pregnancy. While pregnancy terminations have previously been discussed in the absence of data on the safety of the targeted drugs and pregnancy avoidance proposed, with the possibility of many years of benefit from targeted therapy, the concept of new motherhood co-occurring with a diagnosis of NSCLC is being re-examined. While not without controversy, women with advanced lung cancer may pursue adoption or utilization of surrogate gestational carriers.[9,10] Several case reports have emerged describing apparently successful pregnancies in women with advanced lung cancer who began oncogene-targeted therapies before or during early pregnancy.[11-15]

This report describes the incidence, features and outcomes related to pregnancy in oncogene-driven lung cancer and experience with family-building after diagnosis among women of reproductive potential at a single institution.

Material and methods

We defined 18-44 years as ages of reproductive potential. We extracted records of women aged 18-44 years at the time of lung cancer diagnosis who had at least one visit with an oncology provider within our institutional network from January 2010 to June 2021. We then manually reviewed charts for histology, genomic profile and childbearing information. We excluded patients with carcinoid tumors or small cell lung cancer histology.

We excluded patients who lacked information on ALK, ROS1 or EGFR alterations as the essential molecular information required. Additional oncogene data were captured when

available. While not all patients received molecular testing without our system, our institution's protocol covered routine genomic testing for all advanced NSCLC cases, with the assays transitioning over this period from single gene tests to DNA- and RNA-based targeted multiplex NGS.[16] HER2 and MET amplification were also assessed by FISH in cases as clinically indicated.

For quantitative comparisons, we utilized logistic regression for binary outcomes and linear regression for continuous outcomes. Cox proportional hazard ratios were used for survival time comparisons. ALK, EGFR and ROS1 outcomes were assessed relative to the combined outcomes for patients with other/no drivers due to lack of highly effective treatments for other drivers at this time.

Results

78 women aged 18-44 at the time of their initial lung cancer diagnosis consulted with an oncology provider at our institution during the period of study. Sixteen cases were excluded due to carcinoid or small cell histology being present and seven NSCLC cases were excluded due to insufficient oncogene data. Five of these seven had no molecular data due to the clinical scenario not prompting molecular testing at the time, one had insufficient tissue for testing and one stage IV case was only diagnosed as stage IV posthumously. Fifty-five cases of NSCLC with complete oncogene data in women aged 18-44 at diagnosis were identified (see consort diagram in Figure 1). Oncogene drivers were identified in 50/55 (91%) of these women. The five women with no identified oncogene driver had testing for KRAS, BRAF, HER2 and MET exon 14 mutations in addition to testing for EGFR, ALK and ROS1 alterations. Most of these women (48/55, 87%) had advanced, incurable disease at diagnosis requiring systemic therapy (see Table 1).

Fifty-two of the 55 women had available information on childbearing abstractable from the medical records. Nine of 52 women were diagnosed with NSCLC during or within a year of pregnancy (see Table 1, denominators reflect the maximum data available.) Five of the nine women were diagnosed within one year after a pregnancy ended (3 EGFR, 1 KRAS and 1 no driver.) Four of the nine women were pregnant at diagnosis, all of whom had an ALK fusion. Two pregnancies were terminated at the time of cancer diagnosis. A third-trimester pregnancy was induced early at 35 weeks gestational age. One patient was diagnosed based on abnormal findings at time of cesarian section (tumor deposits on ovaries.) An additional patient with ALK driven NSCLC experienced an unplanned pregnancy 8 years after her diagnosis at the time of CNS progression on alectinib; this pregnancy was terminated. All three terminations following a diagnosis of NSCLC were desired pregnancies and termination was performed following a discussion in the context of necessary anti-cancer interventions to preserve maternal life that were considered potentially highly fetotoxic.

Seven of the nine peri-pregnancy diagnoses occurred in the setting of ALK or EGFR drivers. The odds of peri-pregnancy diagnosis was 2.3 times higher for ALK and EFGR compared than other groups, but this difference was not statistically significantly ($p=0.32$.) Women with ALK rearranged NSCLC were significantly younger by an average of 3.9 years compared NSCLC without a known driver ($p=0.02$). While patients with ALK rearranged NSCLC were 3.1 times more likely to be nulliparous than non-ALK driven NSCLC ($p=0.05$), this association did not persist when controlling for age. There were no clear associations between age or nulliparity and other drivers for this small cohort.

Six patients pursued adoption or having a biological child after diagnosis, of which five were nulliparous and one had insufficient data to assess parity. Two patients have adopted children and are alive more than nine years after diagnosis.

Four patients pursued having a biological child through in vitro fertilization (IVF). The first patient had had egg retrieval shortly prior to cancer diagnosis and pregnancy occurred in a gestational surrogate 4 years after her diagnosis, resulting in a healthy infant. The patient died five years after her diagnosis. A second patient underwent oocyte retrieval after diagnosis and prior to treatment; embryos were transferred but did not result in pregnancy in a gestational surrogate. The patient has no evidence of active disease 3.5 years after her diagnosis and is considering an additional egg retrieval. A third patient underwent ovarian stimulation while on entrectinib but lacked further documentation regarding the outcome of egg retrieval. She has no evidence of active disease 2.5 years after her diagnosis. The fourth patient underwent oocyte collection while on alectinib leading to four embryos for which genetic testing was ultimately not possible. A gestational surrogate was selected but embryos had not been transferred at last follow-up with a fertility specialist, which was two months prior to the patient's death. She died 18 months after her cancer diagnosis.

Survival was qualitatively not impacted by peri-pregnancy diagnosis in this small cohort (see Figure 2). Survival differed substantially by oncogene driver (see Figure 3). Median overall survival was 3.4, 1.0 and 1.7 years longer for those with ALK, EGFR or ROS1-driven cancer, respectively, compared to NSCLC with other or no known oncogene driver (p=0.07). Hazard ratios for risk of death compared to other/no driver were 0.17 (95% CI 0.06-0.52) for ALK, 0.32 (95% CI 0.11-0.98) for EGFR and 0.12 (95% CI 0.02-0.98) for ROS1 using Cox proportional hazards. When aggregated, the median overall survival for all three oncogenes with highly effective targeted therapy vs other/no driver was 3.4 years with hazard ratio for risk of death 0.21 (95% CI 0.09-0.51.)

Discussion

Pregnancy around the time of an ALK and EGFR driven lung cancer diagnosis occurred in 17% of our female patients aged 18-44. A direct interplay between the NSCLC and pregnancy is not currently supported. Instead, the intersection is likely due to young age at time of diagnosis relative to NSCLC with no known oncogene drivers. The convergence between motherhood and metastatic oncogene-driven lung cancer is likely to increase in frequency as survival continues to improve. Given that half of women with ALK rearranged lung cancer at our center were not mothers at time of diagnosis and this group frequently experiences prolonged survival, this group is particularly likely to seek options for motherhood. This scenario presents an ethical dilemma for medical providers as outcomes are highly variable. While patients have a life-threatening incurable disease, some may have many years of excellent quality of life, such as the three women who lived at least 11 years after their lung cancer diagnosis within this cohort. We present the third reported case of successful pregnancy via gestational surrogate for a patient with oncogene driven lung cancer as well as two cases of adoption after an incurable lung cancer diagnosis[9,10].

These data are limited by their retrospective nature. The true pregnancy rate may be underestimated in this report due to the unknown incidence of unreported pregnancy loss or terminations given the subclinical nature of many miscarriages and psychosocial barriers to

discussing terminations. The medical record may also not attribute children reliably as biologic or non-biologic children.

Management of lung cancer during pregnancy remains a challenge with sparse case reports on pregnancies carried to term while on targeted therapy. As targeted therapies may differ in terms of their ability to cross the placenta, and the importance of the signaling pathway affected by the drug at different stages of embryogenesis, more detailed information on such cases, supported by non-clinical data are desperately required. In some regions of the United States, the 2022 reversal of Roe vs. Wade may also increase the incidence of pregnancy at the time of lung cancer diagnosis and may prevent termination of pregnancies for preservation of maternal life in women on targeted therapies. This potential further highlights the need for proactively gathering comprehensive information on of the intersection of motherhood and the treatment of oncogene-driven NSCLC. Two registries on pregnancy in cancer are actively collecting case data. The International Network of Cancer, Infertility and Pregnancy (INCIP) based in Europe collects data from participating institutions from around the world.[17] Non-participating institutions may contact INCIP for enrollment via the website www.cancerinpregnancy.org. The Cancer and Pregnancy Registry based in the United States collects data from individual patients. Patients may contact the registry at https://cancerandpregnancy.com/.[18]

Clinical Practice Points

Limited case report data are available describing pregnancy and motherhood in oncogene-driven NSCLC, which is likely to become more common as survival for advanced NSCLC increases. We found that 9/55 (16%) of the women of child-bearing age treated at our institution for NSCLC over 2010-2021 were pregnant at the time of diagnosis and/or pursued having a child after a diagnosis while on targeted therapy. Similar to prior reports, in our series, early pregnancies at or after diagnosis were terminated and a later pregnancy was delivered pre-term to avoid fetal exposure to targeted therapy. Gestational surrogacy and adoption are feasible for women with oncogene-driven NSCLC. Effects of targeted therapies on pregnancy remains understudied. Patients and providers are encouraged to register cases of pregnancy in cancer in one of two available registries, either via an institution affiliated with the International Network of Cancer, Infertility and Pregnancy (see www.cancerinpregnancy.org) or direct patient contact with the Cancer and Pregnancy registry at https://cancerandpregnancy.com/.

Acknowledgements

We acknowledge the assistance of Amy Walde in procuring data from the UCHealth Cancer Registry. The work of DRC was partially supported by the University of Colorado Cancer Center's Thoracic Oncology Research Initiative and the Joyce Zeff Chair in Lung Cancer Research.

Figures and Tables

Figure 1: Consort diagram. Women of reproductive potential diagnosed with lung cancer 2010-2021 at a single institution

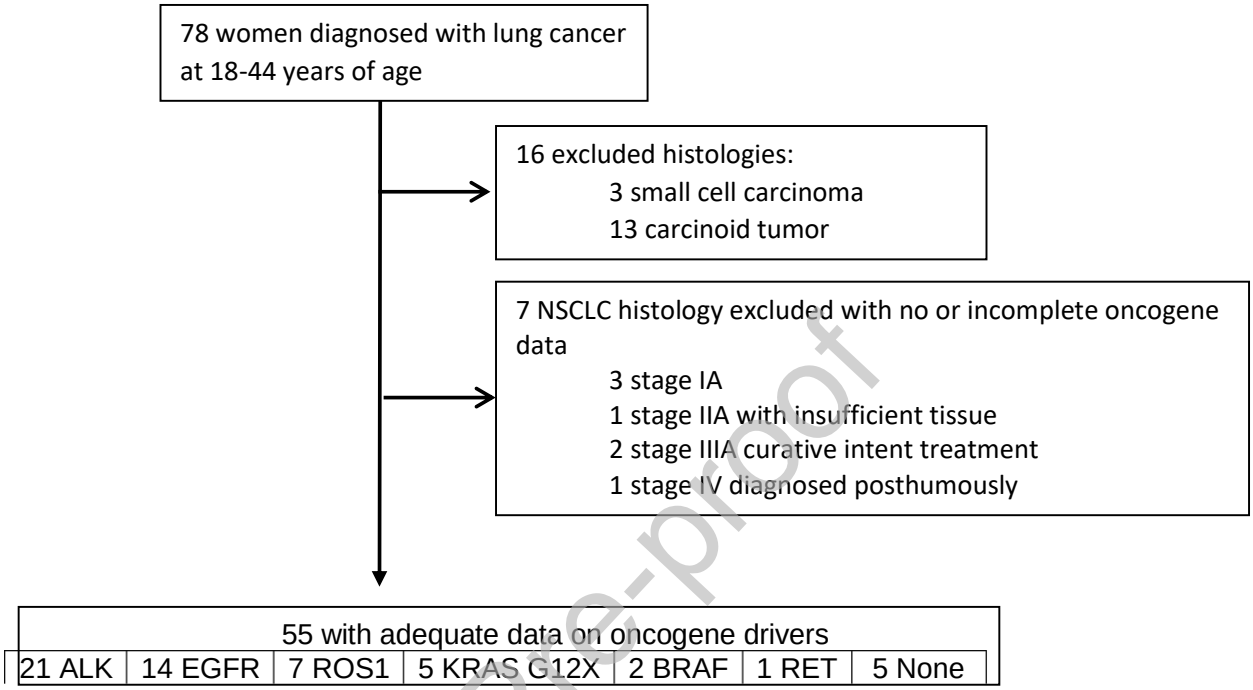


Table 1: Diagnosis of NSCLC in relation to parity, peri-pregnancy diagnosis, and family building after diagnosis

Altered oncogene	N (55 total)	Median age at diagnosis (range) (N=55)	Percent advanced stage* (N=55)	Nulliparous at diagnosis (N=51)	Number diagnosed in peri-pregnancy period (N=52)	Adoption or IVF after diagnosis**	Median overall survival among advanced disease (range) (N=48)
ALK	21	34 (25-44)	90%	11/20 (55%)	4/21 (19%)	4	3.4 years (8 months-11.9 years)
EGFR	14	38 (27-44)	86%	4/14 (29%)	3/14 (21%)	1	2.6 years (2 months-6.6 years)
ROS1	7	36 (22-40)	100%	2/5 (40%)	0/6	1	2.9 (5 months-7.8 years)
Other	8	40 (24-43)	75%	3/8 (38%)	1/8 (13%)	0	8 months (2 months-3.9 years)
None	5	42 (30-44)	80%	0/4	1/4 (25%)	0	1.5 years (1 year-3.4 years)

*Unresectable stage III or stage IV lung cancer

**Six women with advanced stage lung cancer spontaneously reported that they pursued IVF via gestational surrogate or adopted a child. Adoption and surrogacy are not routinely assessed by all providers within the institutional network.

Figure 3: Overall survival of women 18-44 with advanced lung cancer by peri-pregnancy diagnosis (N=48)

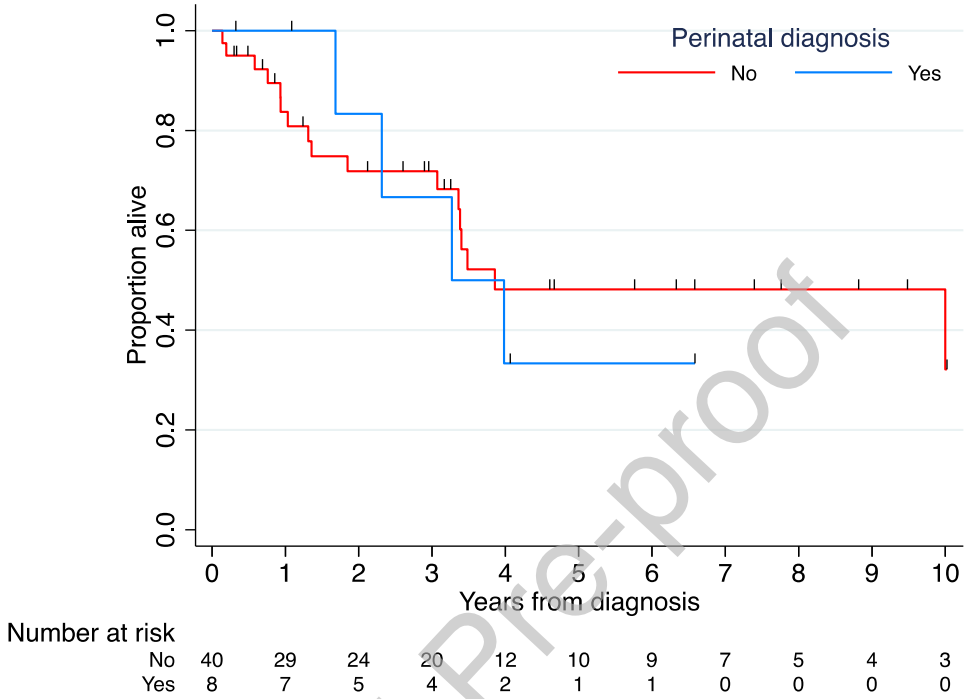
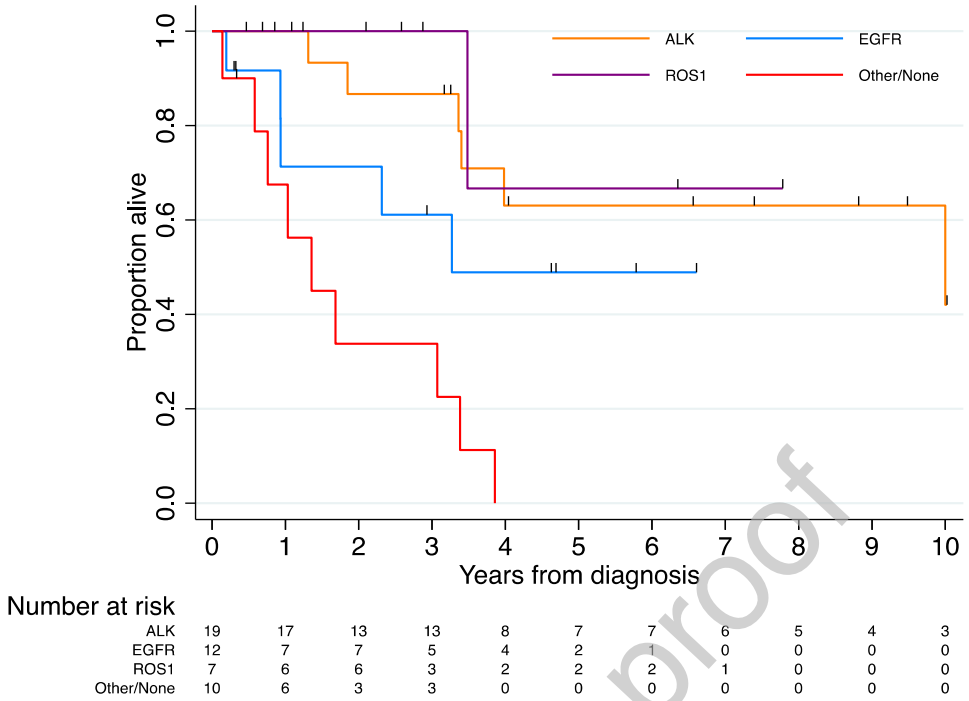


Figure 2: Overall survival of women 18-44 with advanced lung cancer by oncogene driver (N=48)



Note: Data truncated at 10 years. One woman with ALK rearranged lung cancer died 11 years after diagnosis and two women with ALK rearranged lung cancer are still alive >11.5 years after diagnosis.

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