

Does Lung Adenocarcinoma Subtyping Offer Clinical Benefits? A Population-Based Study from Sweden

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ABSTRACT

Purpose: Classification of lung adenocarcinoma into subtypes is relatively recent and not universally practiced. Consequently, large representative studies describing clinical outcomes are rare, failing to pervasively present advantages of subtyping. We describe the situation in Sweden with focus on survival.

Methods: Patient data were obtained from the Swedish cancer registry from 2005 to 2021 accounting for 1418 patients, less than 5% of the reference group ‘adenocarcinoma not otherwise specified (NOS)’. Non-parametric survival estimates were calculated using the Kaplan-Meier method and testing for linear consistency using Weibull modelling.

Results: Survival was generally better for women compared to men and this was most prominent for early-stage cancers. Female 5-year survival decreased in order, lepidic (59%), papillary (51%), invasive mucinous (46%), colloid (36%) and adenocarcinoma NOS (24%). Male 5-year survival for lepidic (46%) and colloid subtypes (22%) was significantly lower than female survival. Survival slopes for T1, T2, N0, M0 cases of lepidic, papillary and adenocarcinoma NOS were almost linear, in agreement with Weibull modelling k-values of 1.00 or slightly higher, implying that mortality increased slowly with time.

Conclusions: The results showed female survival advantage for all adenocarcinoma subtypes. Survival in T1 and T2 classes with N0 and M0 for lepidic, papillary and adenocarcinoma NOS was close to linear, suggesting that patients are homogeneously diagnosed and treated. Survival benefits of lepidic and papillary subtypes over adenocarcinoma NOS give justification for adenocarcinoma subclassification, and also an independent validation of the WHO 2021 adenocarcinoma grading classification specifying lepidic and papillary subtypes.

Introduction

Survival in lung cancer (LC) has generally increased due to early diagnosis, improvements in treatment and changing histology towards the relatively less fatal adenocarcinoma (1, 2). Increase in adenocarcinoma compared to other histological types of LC has been a universal trend; by 2020 adenocarcinoma had become the most common male LC histology in most countries and female histology in all countries (3), possibly due to decreasing smoking rates as adenocarcinoma is less associated with smoking than the other histologies. Due to the prominence of adenocarcinoma, World Health Organization (WHO) has introduced several modifications to the histological classification of adenocarcinoma since 1967 (4, 5).

In 2011 two survival studies on early-stage adenocarcinoma were published from the USA (N=210) and Australia (N=514, stage I) describing survival differences for adenocarcinoma subtypes (4, 6). Such results were used in the 2015 WHO classification distinguishing lepidic, acinar, papillary, micropapillary and solid types defined by predominant growth pattern in biopsies and cytology specimens (7, 8). The subtypes differ by presentation and prognosis, lepidic presenting in low-grade with a good prognosis, acinar and papillary with intermediate grade and prognosis and lastly micropapillary and solid with high grade and poor prognosis (8, 9). In the 2021 WHO classification the distinctions between adenocarcinoma subtypes were further refined by introducing a 3-tiered grading system based on predominant histological high-grade patterns (10).

Practical adaptation of the adenocarcinoma subclassification in global thorax clinics has been variable. A recent review listed 65 studies reporting on the subtyping but the results were inconsistent, for example on relative abundance (11). Although refined subtypes were introduced to confer prognostic and therapeutic information, clinical judgements still largely rely on stage, mutational profile and PD-L1 status (5, 12). Recently, DNA methylation patterns have been proposed to provide further therapeutic information (13). The above survival studies published in 2011 on adenocarcinoma subtypes were replicated in 2022 in a smaller UK study of 262 patients (14). Among the larger studies, adenocarcinoma patients were pooled from several clinical trials and 575 patients were assigned histological subtypes (15). Overall survival did not differ between the subtypes but lepidic and acinar/papillary

showed higher disease-free survival than micropapillary/solid types. A Chinese study on 2268 adenocarcinomas analyzed lymph node involvement in the subtypes (16). In 47% of patients with solid and micropapillary types, nodal involvement was observed and this decreased to an intermediary level in patients with papillary and acinar subtypes and to 0% in lepidic patients. Survival in individual adenocarcinoma subtypes has been analyzed in several large studies based on the Surveillance, Epidemiology, and End Results (SEER) database covering lepidic, invasive mucinous, acinar, colloid and papillary types (17-22). Among 600 patients with defined adenocarcinoma subtypes, major genetic pathways and possible drug targets were characterized (23). A detailed genomic and proteomic analysis of 103 Chinese adenocarcinoma subtypes was published (24).

The variable adaptation of the WHO subtype classifications in clinical practice reflects doubts about their benefits. One obvious way to test the benefits would be to show that the classification results in homogeneous patient population with uniform survival kinetics which can be assessed e.g., using the Weibull regression model (25, 26). In fact, none of the above cited articles show such stage-specific kinetics. In the present study we collected adenocarcinoma subtypes in patients from the Swedish cancer registry in ages 23-93 years between years 2005 and 2021. The available subtypes were lepidic, papillary, invasive mucinous and colloid adenocarcinoma which we compared to adenocarcinoma NOS (not otherwise specified). We report periodic sex-age-stage histological distributions and overall survival in these patients, with a specific aim to test for homogeneity in survival outcomes, ascertained by survival kinetics fitted with the Weibull distribution (25, 26).

Methods

Patients diagnosed with LC were identified from the Swedish cancer registry between years 2005 and 2021 using ICD-7 code 1621- ‘LC specified as primary’. The cancer registry has a very high rate (98%) of morphological verification by pathologists (27). Data on 30,780 patients with adenocarcinoma were available, and 1418 of these had information on subtype. The individual histological subtypes were defined by ICD-O-3 classification (5-digit code) and the following subtypes were included: papillary adenocarcinoma (82603), colloid adenocarcinoma (84803), bronchioloalveolar cancer not otherwise specified (82503) and bronchioloalveolar carcinoma mucinous (82533); the latter two were labelled according to the WHO 2015 terminology to ‘lepidic’ and ‘invasive mucinous’, respectively (7, 10). We noted that the cancer registry did not receive adenocarcinoma subtype information geographically uniformly from Sweden. While 22% of adenocarcinoma NOS data originated from Stockholm (the capital), those for the subtypes were between 32 to 52% from Stockholm. In order to secure regional balance in the origins of adenocarcinoma NOS we tested that survival was equal between Stockholm and the rest of the country.

Only first LC cancer for each patient was included in the analysis. The earliest diagnostic year for the invasive mucinous subtype the earliest year was 2012 (median 2019). The other histologies were available since beginning of study period (2005). The analysis excluded patients with multiple LCs at the first diagnosis date, with tumors of T classes Tis and T0, and with tumors discovered at autopsy; also excluded were patients with a diagnosis date prior to immigration to Sweden. The cancer registry does not include cancers from the cause of death notifications (27).

Non-parametric survival estimates were calculated by the Kaplan-Meier method using the survminer package in R. Survival data were also modelled parametrically using the Weibull distribution (28), where hazard function is parametrized as:

$$h(t) = \frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{(k-1)}$$

The interpretation of the Weibull shape parameter (k):

k < 1 (decreasing mortality): initial high mortality as vulnerable individuals die;

k = 1 (constant mortality): mortality due to random external events, no inherent aging;

k > 1 (increasing mortality): mortality increases over time for late events and/or aging.

In addition to adenocarcinoma NOS stages 1 and 2, we modelled also stages 3 and 4, as well as elderly in overall background population with the Weibull distribution.

Distribution of T stages between sexes was compared by Fischer exact test with Benjamini-Hochberg correction for multiple comparisons.

All statistical analyses and data visualization were done using SAS and R (version 4.4.0). Differences were considered significant when their 95% confidence intervals (CIs) were non-overlapping.

Results

The summary of the studied cohort is shown in **Table 1** with dominant adenocarcinoma NOS (13,734 male and 17,046 female patients). All adenocarcinoma subtypes (N=1418) were more common in women compared to men: case numbers decreased in order lepidic>colloid>invasive mucinous>papillary; however, case numbers are influenced by changes in subtypes of classification and its adoption and do not reflect true subtype distribution in adenocarcinoma patients. The subtypes accounted for less than 5% of the adenocarcinoma NOS patients. Median diagnostic ages were around 70 years for all.

The extent of tumor growth (T-stage) at time of diagnosis was distributed differently across histologies (**Fig. 1**). In adenocarcinoma NOS, about 33% was T4, 28% was T1, 27% was T2 and 12% was T3. In the lepidic subtype, T1 cases dominated (51%). The majority of patients with papillary and colloid subtypes were diagnosed at T1 and T2; T4 was the most frequent stage in invasive mucinous adenocarcinoma (40 %). Women were more likely than men diagnosed with T1 in adenocarcinoma NOS (25% vs 29%, p<0.001 for T distribution difference) and colloid (23% vs 35%, p=0.0432), for other subtypes the T- stage distribution was not significantly different across sexes (p>0.05 for each histology, Fisher’s exact test adjusted for multiple comparisons). The distribution of N- and M-stages are shown in **Supplementary Table 1**. N0 and M0 were the most common stages for all subtypes.

Kaplan-Meier survival curves by sex and histology (**Fig. 2**) revealed different survival patterns between the histological subtypes and showed a female survival advantage. Data allowing, survival curves are plotted up to 200 months (16.7 years), with vertical lines for 1, 5 and 10 years. Survival in lepidic and papillary adenocarcinoma was similar during first years of follow-up but later lepidic patients survived better. Patients with invasive mucinous survived better than colloid or adenocarcinoma NOS patients; for the latter two, male 50% survival was about 1 year.

Survival at 1 and 5 years after diagnosis is shown in **Supplementary Table 2**. It documents a significant female advantage in survival at year 1 and 5 for adenocarcinoma NOS and lepidic type, and also at year 5 for colloid types. 5-year survival (female/male) was 0.24/0.17 for adenosquamous NOS, 0.59/0.46 for lepidic, 0.51/0.36 for papillary, 0.46/0.39 for invasive mucinous and 0.36/0.22 for colloid types.

Survival curves for each subtype were further assessed by T stage (**Fig. 3**). A striking feature for lepidic and papillary T1 survival plots was their apparent linearity. In T1, 5-year survival for lepidic patients was 80%, for invasive mucinous 75%, for papillary 65%, for colloid 55% and lowest for adenocarcinoma NOS 45%. Advanced T stages were associated with worse survival and for T4 1-year survival was equal for lepidic, papillary and invasive mucinous (55%) types and lower in colloid (35%) and adenocarcinoma NOS (30%). 5-year survival in T4 was about 20% for lepidic, papillary and invasive mucinous types, 10% for adenocarcinoma NOS but only 1% in colloid adenocarcinoma. Survival by T stage is shown sex-specific in **Supplementary Fig. 1**. Female survival was better than male survival for the lepidic type at all stages and for colloid adenocarcinoma at T1 and T2. For the other subtypes female advantage was clear for T1.

As the above figures were generated for all subtypes, we further refined survival analysis for T1 (top) and T2 (bottom) considering only cases with N0 and M0 (**Supplementary Fig. 2**). For T1, all female survival curves, except for colloid subtype, were visually linear, as were male plots for lepidic and papillary subtypes. Case numbers for T2 were lower and the interpretation was less clear; however, lepidic survival for men and women was close to linear up to 10 years, similar to female survival for the colloid subtype.

The data were modelled further using the Weibull distribution; the plots for males and females, and for T1 and T2 (N0, M0) are shown in **Fig. 4** with Weibull shape parameter k. The solid lines show Weibull fits to the data. Data are shown up to 200 months, except for some papillary and colloid sets with few cases. Because of low case numbers no data for invasive mucinous type were shown. For adenocarcinoma NOS male and female T1 k-values were slightly over 1.00 (1.09 and 1.26) while k-values for T2 cases were essentially 1.00. For lepidic type, all k-values were above 1.00 (except male T2, 0.91). For papillary type, case numbers were few and k-values were high. For colloid type, all k-values were below 1.00, except for female T2 (1.40).

As comparison we show Weibull modelled survival data for T3 and T4 (N0, M0) adenocarcinoma NOS (**Supplementary Fig. 3**). At longer follow-up times for T3 cases the model fits were not optimal. For T3 cases k-values were about 0.9 and for T4 cases they were 0.85.

As a second comparison we wanted to test Weibull distribution for individuals in background population, 60-year and 80-year-old at the beginning of the follow-up (**Supplementary Fig. 4**). Model fits were excellent as they superimposed the empirical estimates. For 60-year-olds k-values were 1.46 for men and women. For 80-year-olds, female k-values was higher than the male one (1.52 vs 1.30).

Discussion

Diagnostic classification aims to define homogeneous subgroups that could be similarly treated and that would have identical outcomes. In cancer, TNM classification has been developed and improved for that purpose, and it has proven clinical merits, also in LC. We tested here WHO defined subtypes for uniform survival kinetics and for homogeneity using the Weibull distribution for fitted survival curves. Four subtypes were included, lepidic, papillary, invasive mucinous and colloid, and these were compared to adenocarcinoma NOS. For invasive mucinous and adenocarcinoma NOS, T4 stages were commonest while for the others T1 (lepidic) or T1 and T2 were the commonest stages at diagnosis. Accordingly, lepidic type showed the best 5-year survival of 0.59 for women who generally survived better than men (**Supplementary Table 2**). Papillary and invasive mucinous had about equal survival (0.51 and 0.46 among women); women with colloid type (0.35) survived somewhat better than those with adenocarcinoma NOS (0.24).

Survival curves for adenocarcinoma subtypes were typically curvilinear as is known for cancers in general (**Fig. 2**). They start with a steep decline when fatally ill patients are dying and then bend for a more linear slope when surviving patients are slowly dying. However, when we analyzed survival data by T stage, survival slopes for T1 of the lepidic and papillary types for both sexes were almost straight lines (**Fig. 3**). We then continued for all subtypes considering T1 and T2 classes with N0 and M0 and found a consistent tendency towards linear survival slopes (up to 200 months, 17 years, **Fig. 4**). The likely explanation is that patients diagnosed with T1 and T2 lacking metastasis are relatively homogeneous groups for whom treatment has been successful and who die in age-related stochastic (random) process unrelated to their adenocarcinoma. We searched global LC literature for previous evidence on linear type of survival experience in LC but all data even on localized adenocarcinoma of N0, M0 showed bending slopes with relatively steep initial decline (29, 30). However a large Chinese study on stage I LC showed a linear survival up to 10 years until 2018, however without further comments (31).

Weibull modelling on healthy 60-year old men and women showed almost linear survival rates with Weibull k-values of 1.46; for 80-year-old healthy persons k-values were 1.30 (men) and (1.52) and survival curves modestly bended after more than 10 years of follow-up most likely due to age-related mortality. Weibull k-values for lepidic and papillary T1 and T2 stages (N0, M0) were largely over 1.00 although case numbers for papillary cases were low and model fits were not optimal (**Fig. 4**). In the same analysis male and female k-values for T1 adenocarcinoma NOS were marginally positive (1.09 and 1.26) while for T2 they were 0.98 and 1.00. In T3 and T4 adenocarcinoma NOS k-values were below 1.00 (**Supplementary Fig. 3**).

Large survival studies have been published from the SEER database but often considering a single subtype. For lepidic patients 50% survival has been reported to vary between 30 months and over 80 months which is in the range that we observed (**Fig. 2**) (20, 21). For colloid type the SEER study separated patients undergoing surgery (57%) whose 50% survival was over 80 months compared to those without surgery of 15 months (22). Our data were over 10 months for men and under 20 months for women (**Fig. 2**). For papillary type the SEER data gave 50% survival at 25 months, compared to our 40 and 60 months for men and women, respectively (17).

WHO has revised the classification of adenocarcinoma many times; in the 2004 publication 'adenocarcinoma mixed subtype' was the most frequent subtype representing 80% of all (32). A further connotation was that adenocarcinomas presenting purely a single subtype were uncommon (32). In later WHO classifications the subtypes were further refined but apparently both thorax clinics and cancer registries have not systematically followed these

classifications. For example, the recent European Society of Medical Oncology (ESMO) clinical guidelines on LC make only a statement that ‘for adenocarcinoma morphological features should be clearly presented’ (33).

The limited subtyping of adenocarcinoma in Sweden and lacking of subtypes such as acinar, is also the main limitation of the present study reducing the study population. However, we could include lepidic and papillary subtypes which are included (with acinar type) as sentinel histologies in the WHO 2021 grading classification of invasive nonmucinous adenocarcinomas (10). We have no guarantee about diagnostic consistency as the definitions of subtypes may have shifted in the course of the 16 years covered, in response to the WHO classification changes. In this regard it may be an advantage that relatively large number of samples were obtained from the Stockholm area, dominated by Karolinska University Hospital, assuming the classification principles were easier to keep uniform in a few locations than in the whole country.

In conclusion, we documented female survival advantage for all adenocarcinoma subtypes. Survival declined in order lepidic, papillary, invasive mucous, colloid and adenocarcinoma NOS. Survival in T1 stage was superior and T4 inferior for all subtypes. Survival in T1 and T2 classes with N0 and M0 for lepidic, papillary and adenocarcinoma NOS types was close to linear and the Weibull k-values were 1.00 or slightly higher (except for papillary type with small case numbers), suggesting that patients are homogeneously diagnosed and treated. Survival benefits of lepidic and papillary subtypes over adenocarcinoma NOS give justification for adenocarcinoma subclassification and also give an independent validation of the WHO 2021 adenocarcinoma grading classification (10). Lung adenocarcinoma remains a life-threatening disease and better recognition of adenocarcinoma subtypes, together with molecular and clinical data, could help individualize treatment combinations for each patient.

ADDITIONAL INFORMATION

DATA AVAILABILITY

Availability of data and materials

The data that support the findings of this study are available from the corresponding author and with permission of the Swedish health authority upon reasonable request.

ETHICS

The study was approved by the Regional Ethical Review Board in Lund University, February 6, 2013 (Reference 2012/795 and subsequent amendments). The Regional Ethical Review Board in Lund University waived the need to include informed consent. The study was conducted in accordance to the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Design: KH

Acquisition of data: KS, JS, FZ, KH

Statistical analysis and interpretation: KH, FZ, AF, AH

Manuscript writing: KH and all other authors.

Approval of the final text: All authors

CONFLICT OF INTEREST

A.H. is shareholder in Circio Holdings ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

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CLINICAL TRIAL NUMBER

Clinical trial number: not applicable.

LEGENDS TO FIGURES

Fig. 1. Distribution of T-stages according to histology.

Fig. 2. Kaplan-Meier survival analysis by sex and histology. The dashed vertical lines mark 1-, 5- and 10-year time points.

Fig. 3. Survival curves for each adenocarcinoma subtype by T stage. The dashed vertical lines mark 1-, 5- and 10-year time points.

Fig. 4. Fitting Weibull survival distribution model to adenocarcinoma subtypes (blue line), superimposed on empirical Kaplan-Meier survival estimates. Weibull shape parameter k is shown for each subgroup.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Sex-specific survival in lung adenocarcinoma subtypes by T stage; male (upper row), female (lower row).

Supplementary Figure 2. Sex specific survival in lung adenocarcinoma subtypes for T1 (top) and T2 (bottom) stages only considering cases with N0 and M0.

Supplementary Fig. 3. Weibull modelled survival data for T3 and T4 (N0, M0) adenocarcinoma NOS.

Supplementary Fig. 4. Weibull modelled survival data for health 60-year and 80-year-old individuals.

Supplementary Table 1. Case numbers by N and M stage for lung adenocarcinoma subtypes.

Supplementary Table 2. 1-year and 5-year overall survival estimates (Kaplan-Meier) by sex and histology. Marked (*) significantly different estimates between sexes.

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Table 1. Summary of the analyzed cohort with cases diagnosed between 2005 and 2011^{1,2}.

Histology	Males N	Females N (%)	Age at diagnosis Median [25- 75 %]
Adenocarcinoma NOS	13734	17046 (55.4 %)	71 [64 77]
Lepidic	273	396 (59.2 %)	70 [64 75]
Papillary	53	88 (62.4 %)	70 [63 75]
Invasive mucinous	80	121 (60.2 %)	71 [63 77]
Colloid	183	224 (55.0 %)	69 [63 75]
Total (other than adenoca)	589	829	

Fig. 1

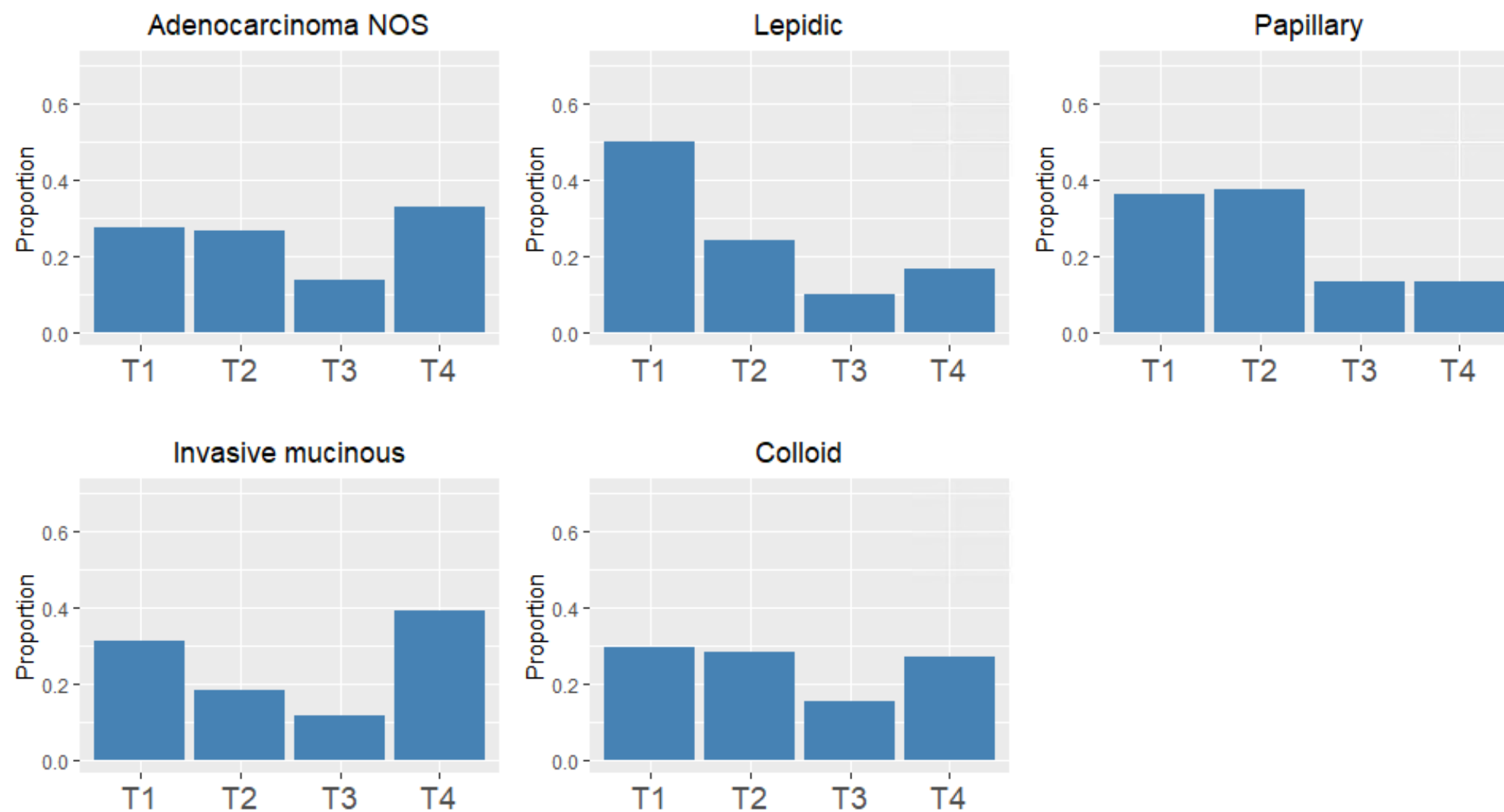


Fig. 2

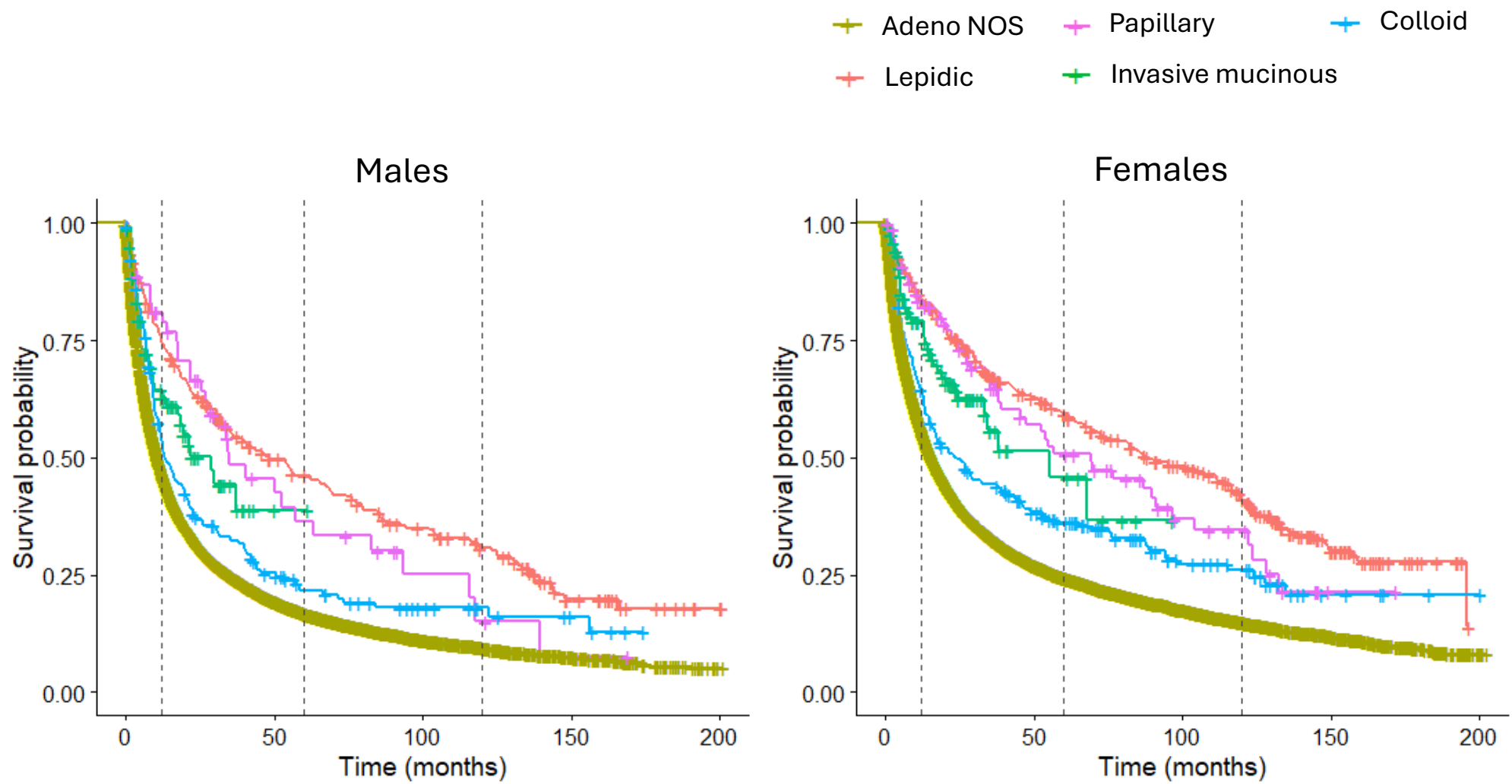


Fig. 3

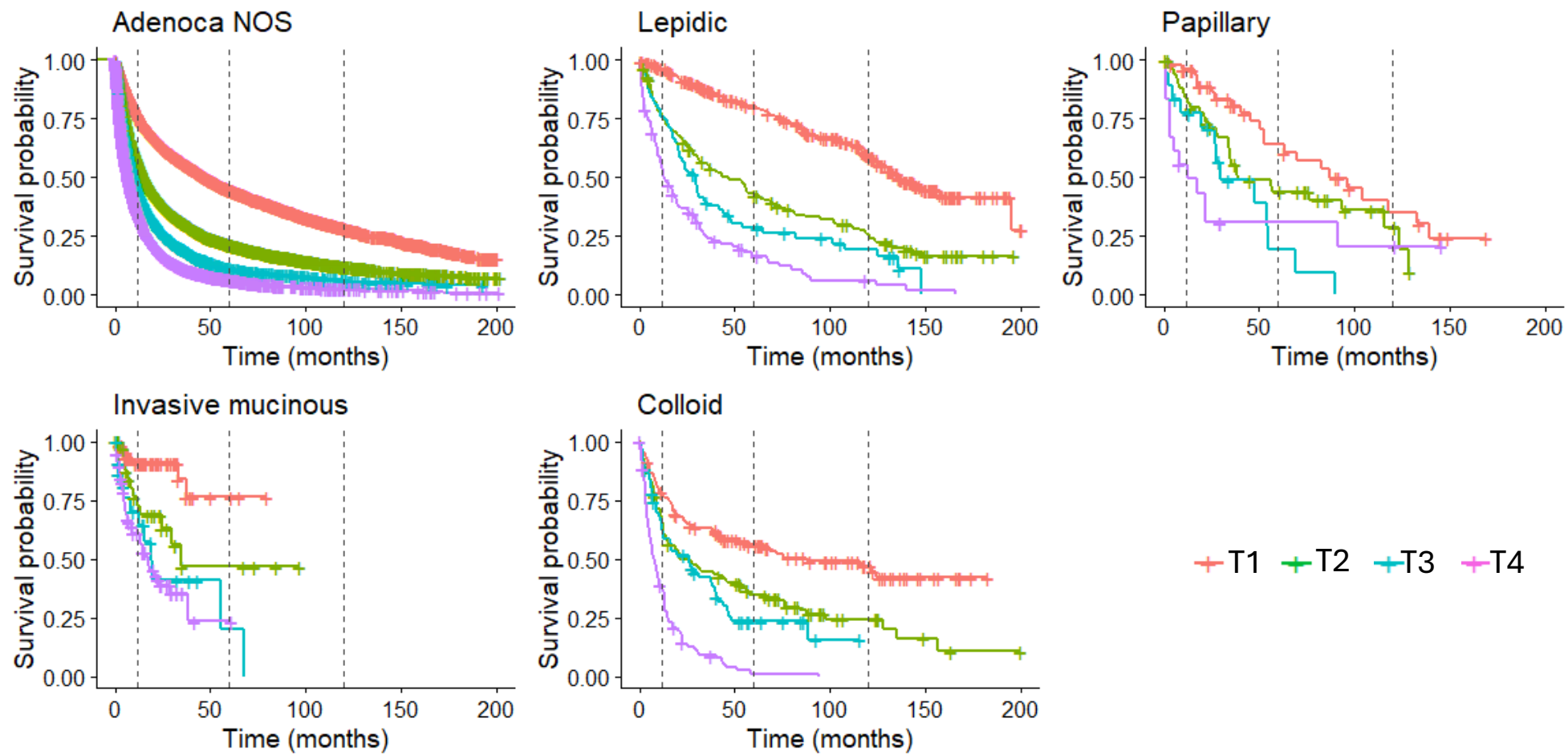
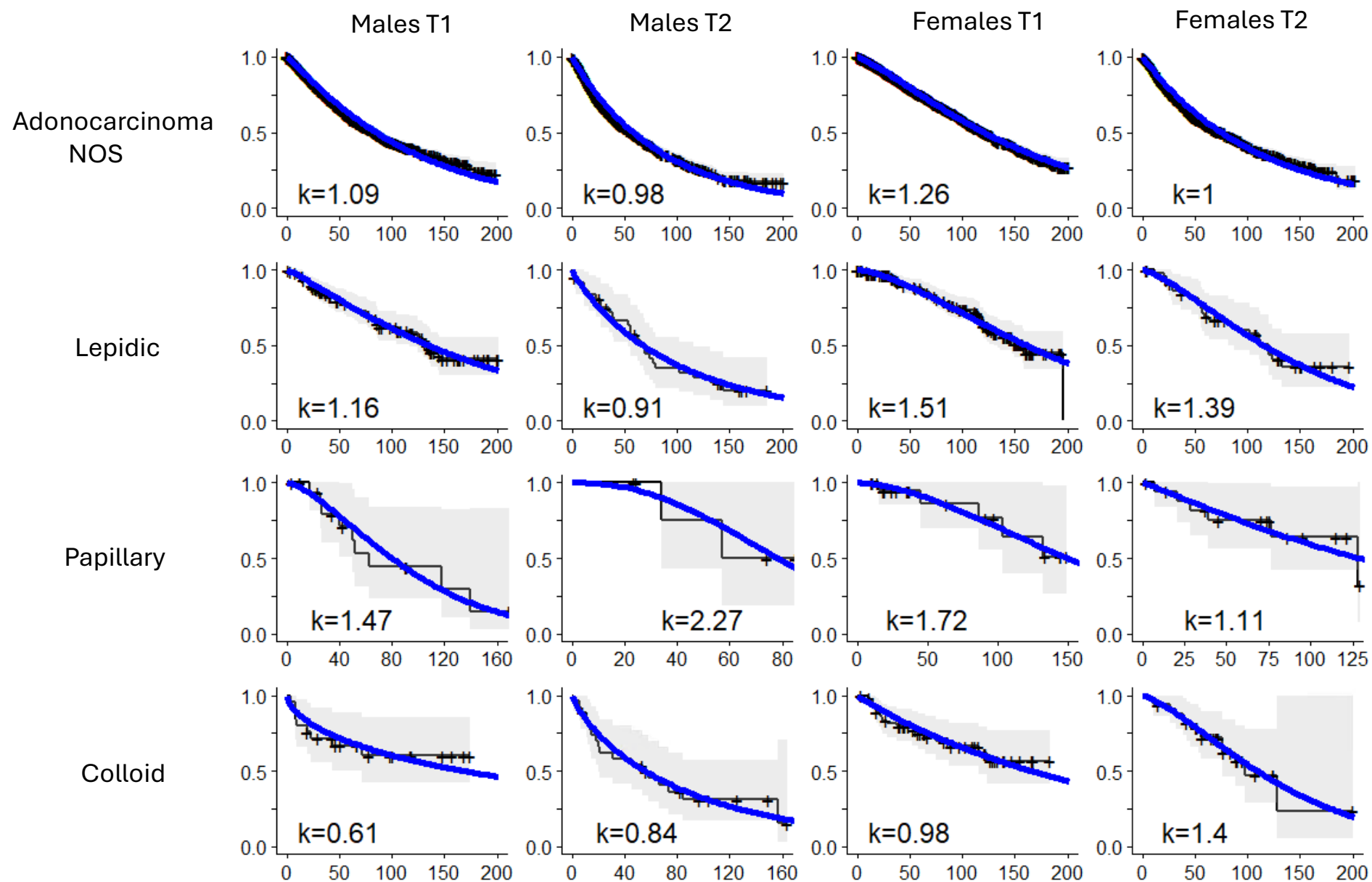
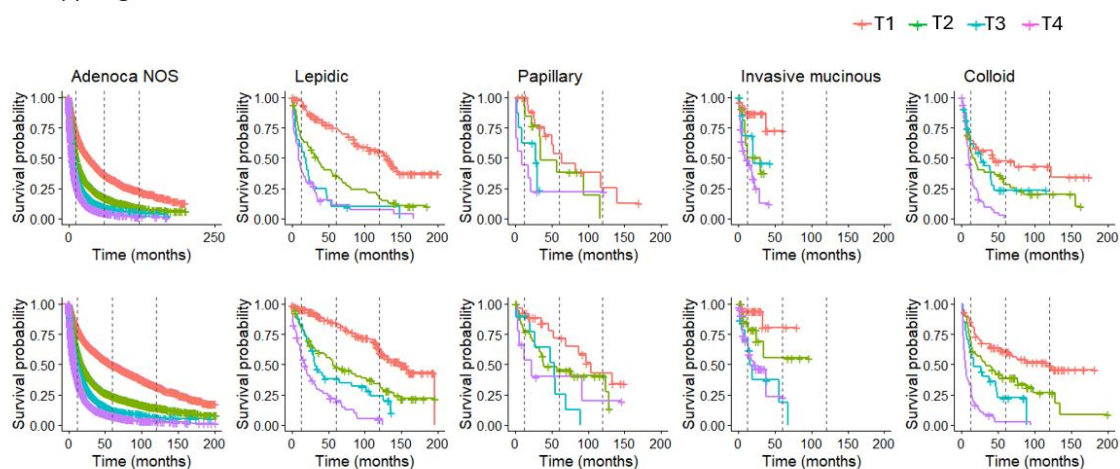


Fig. 4



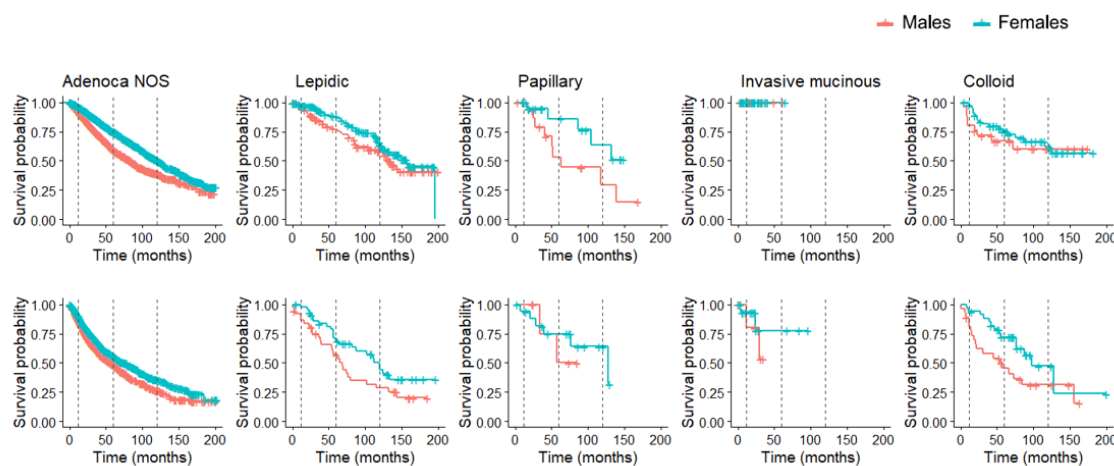
Supplementary Figure 1. Sex-specific survival in lung adenocarcinoma subtypes by T stage; male (upper row), female (lower row).

Suppl Fig. 1



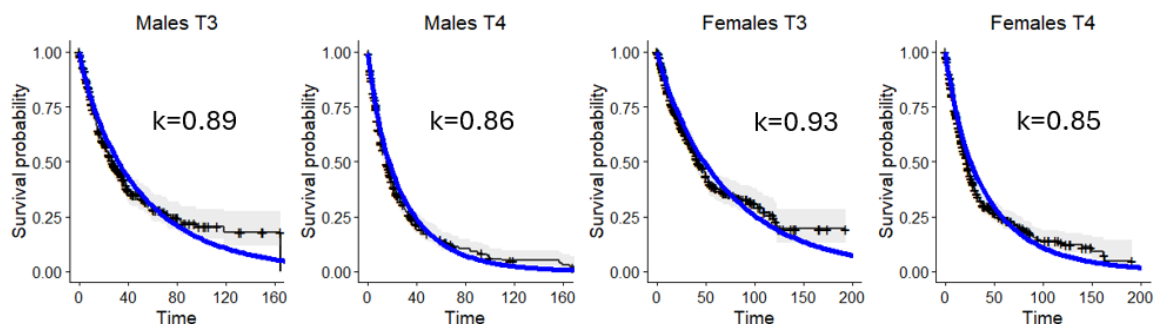
Supplementary Figure 2. Survival in adenocarcinoma subtypes without metastases (N0 and M0) in stages T1 (upper row) and T2 (lower row). The dashed vertical lines mark 1-, 5- and 10-year time points.

Suppl. Fig. 2



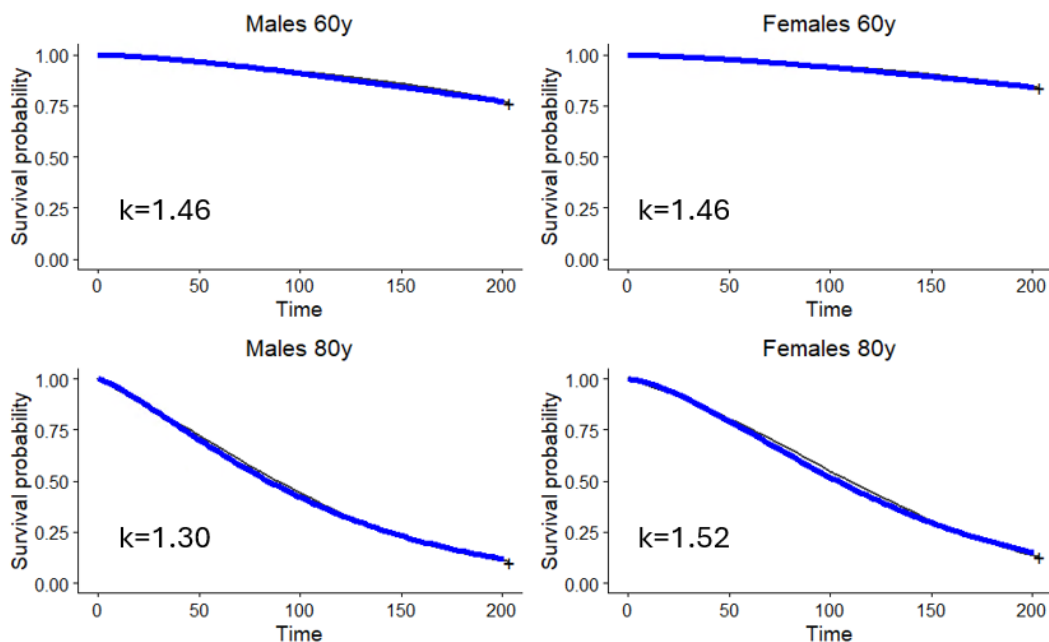
Supplementary Figure 3. Fitting Weibull survival distribution model to adenocarcinoma NOS T3-T4 subcohorts (blue line), superimposed on empirical Kaplan-Meier survival estimates. Weibull shape parameter k is shown for each subgroup.

Suppl Fig.3



Supplementary Figure 4. Fitting Weibull survival distribution model to background Swedish population, random sample of 10 000 individuals who were 60 and 80 years old, respectively, at the beginning of follow-up period (1st January 2025) (blue line), superimposed on empirical Kaplan-Meier survival estimates. Weibull shape parameter k is shown for each subgroup.

Suppl Fig.4



Supplementary Table 1 Case numbers by N and M stage for histological subtypes.

N stage distribution (N)

Histology	N0	N1	N2	N3	Nx	N missing
Adenocarcinoma NOS	12137	2262	842	6694	865	669
Lepidic	526	34	34	23	10	20
Papillary	89	11	21	14	2	4
Invasive mucinous	131	14	27	23	4	7
Colloid	251	21	76	40	12	7

M stage distribution (N)

Histology	M0	M1	Mx	M missing
Adenocarcinoma NOS	13121	16507	234	907
Lepidic	469	161	11	28
Papillary	105	28	3	5
Invasive mucinous	232	160	7	8
Colloid	232	160	7	8

Supplementary Table 2 1-year and 5-year overall survival estimates (Kaplan-Meier) by sex and histology. Marked (*) non-overlapping 95%CI for estimates between sexes.

Males survival

Histology	N at risk	1-year survival		5-year survival	
Adenocarcinoma NOS	13734	0.47	[0.47 - 0.48]*	0.17	[0.16 - 0.18]*
Lepidic	273	0.75	[0.70 - 0.80] *	0.46	[0.40 - 0.53] *
Papillary	53	0.81	[0.71 - 0.92]	0.36	[0.24 - 0.55]
Invasive mucinous	80	0.64	[0.54 - 0.77]	0.39	[0.26 - 0.58]
Colloid	183	0.55	[0.48 - 0.62]	0.22	[0.16 - 0.29] *

Females survival

Histology	N at risk	1-year survival		5-year survival	
Adenocarcinoma NOS	17046	0.56	[0.56 – 0.58] *	0.24	[0.24 – 0.25]*
Lepidic	396	0.84	[0.81 - 0.88] *	0.59	[0.55 - 0.65] *
Papillary	88	0.84	[0.76 - 0.92]	0.51	[0.40 - 0.64]
Invasive mucinous	121	0.79	[0.72 - 0.87]	0.46	[0.32 - 0.66]
Colloid	224	0.65	[0.59 - 0.71]	0.36	[0.30 - 0.43] *