Mortality Following Long-term Lung Cancer Survival

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INTRODUCTION

Many medical directors believe the excess mortality of most malignancies will follow a pattern consistent with a temporary flat extra. That is to say, the extra mortality will be very high in the early years after treatment (higher than can be matched by a table rating), but then returning to standard mortality rates, often within 5 years. Another belief expressed by many medical directors is that even with the worst cancers, or perhaps especially with the worst cancers, the rare survivor who lives more than 10 or 12 years beyond treatment can be considered a standard risk. Notable exceptions include breast cancer with its predilection for late recurrences and secondary primaries.

It appears to us that lung cancer should be added as an exception. Our analysis of lung cancer cases from the Surveillance Epidemiology and End-Results (SEER) ''Limited-Use'' database confirms that early mortality is incredibly high and even after 10 or more years of survival; the excess mortality is still very significant.

METHODS

The SEER is a program managed by the National Cancer Institute (NCI). SEER data has been collected since 1973 from 7 founding cancer registries.[1] Seattle was added in 1974 and Atlanta in 1975. More recent additions were in 1992 and 2000.[2] The data includes de-identified but otherwise seriatim data with details about newly diagnosed cancer cases and follow-up information including date and cause of death. This re-

Table 1. Distributions and Characteristics

Age	N	% Male	% Surgery	% Radiation	Exposure (person-yrs)	Deaths	5-Year Survival (%)	10-Year Survival (%)
40–44	5554	54.7	26.3	55.6	12,120.2	4557	18.6	15.0
45–49	11,439	56.5	26.1	53.4	23,914.3	9610	17.3	12.9
50–54	20,023	57.7	25.5	51.6	41,122.9	16,933	16.9	12.3
55–59	30,389	58.3	25.8	49.2	59,712.6	26,024	16.2	10.4
60–64	41,651	59.7	25.0	46.9	78,507.9	36,434	15.0	8.8
65–69	51,759	58.5	24.8	43.7	92,790.3	46,114	13.8	7.2
70–74	54,467	57.1	23.2	39.9	85,346.8	49,390	11.6	5.3
75–79	45,102	55.3	19.1	36.1	59,358.7	41,715	8.8	3.3
80–84	26,719	52.9	12.6	31.4	28,088.6	25,245	6.1	1.8
85+	14,145	49.4	5.5	22.5	10,900.7	13,717	2.8	0.6
Histology								
Small Cell	47,840	52.8	3.7	41.3	54,312.7	45,792	5.1	2.5
Large Cell	18,653	59.4	22.0	51.8	28,765.3	17,203	10.4	6.0
Other Epithelial	64,303	56.5	7.0	39.3	64,719.3	60,648	5.5	2.4
Squamous	66,146	67.6	29.8	48.8	122,840.1	58,823	14.2	7.1
Adenocarcinoma	98,063	51.9	33.3	38.6	197,671.5	83,505	17.4	9.9
Unknown	6243	44.9	21.9	22.8	23,554.1	3,768	44.1	33.9
AJCC Stage								
I: $T_{1-2}N_0M_0$	56,940	53.1	64.3	21.5	217,309.5	38,532	40.1	23.9
II: $T_{1-2}N_1M_0$, $T_3N_0M_0$	10,122	58.5	76.4	43.7	31,623.1	7950	27.4	14.7
IIIA: $T_{1-2}N_2M_0$, $T_3N_{1-2}M_0$	30,730	58.3	27.5	61.4	55,832.9	27,318	12.3	5.9
IIIB: $T_{1-4}N_3M_0$, $T_4N_{1-3}M_0$	56,533	57.5	9.6	47.1	66,527.5	52,947	6.3	3.1
IV: $T_{1-4}N_{1-3}M_1$	118,499	57.9	5.1	46.8	80,086.3	116,083	1.6	0.7
Unstaged	28,424	56.2	6.0	30.0	40,483.7	26,909	7.1	2.9
Grade (differentiation)								
Well	9481	49.8	55.4	26.2	30,915.8	6597	35.8	21.5
Moderate	36,643	58.6	52.2	37.0	98,053.9	28,663	26.0	14.3
Poor	84,093	59.4	30.5	47.5	148,449.9	74,497	13.7	7.4
Anaplastic	35,649	55.1	13.7	45.5	49,461.1	33,567	7.9	4.2
Not reported	135,382	55.8	8.2	39.9	164,982.3	126,415	7.2	4.0
Total	301,248	56.8	21.9	41.9	491,863.0	269,739	12.3	6.8

coded data is available to qualified researchers in a form that NCI now refers to as "limited-use" rather than "public-use" data files.

Our analysis began with the SEER limited-use data released in April 2008. This dataset has mortality follow-up through December 2005. We selected cases of first primary malignancy diagnosed during the years 1988 to 2003 with the Site Recode 22030 (lung and bronchus). We retained only those cases where the age at diagnosis was 40 years or greater.

We further selected on the basis of Histology Recodes 01 (epithelial neoplasms, NOS), 02 (squamous cell neoplasms), and 05 (adenomas and adenocarcinomas). Based on the reported ICD-O-3 histology codes, we assigned each case to 1 of 5 histology groups: small cell, large cell, squamous, other epithelial, and adenocarcinoma.

For stages, we used the modified AJCC values. The term "modified" indicates SEER correction of the reported AJCC stage based on additional information submitted by the regional cancer registry. For tumor grade, we used the standard SEER classifications. Unfortunately, grade was not reported for many cases.

Table 2. Mortality Results by Age Band for First Ten Durations After Diagnosis. Act is Actual Deaths, A/E is The Ratio of Actual to Expected, And EDR is the Excess Death Rate (Deaths Per Thousand Person-Years)

Age		Duration 1	2	3	4	5	6	7	8	9	10	Total
40–44	Act	2880	1040	327	117	67	27	27	26	10	6	4527
	A/E	27822%	19253%	8783%	3960%	2723%	1242%	1424%	1485%	629%	410%	13407%
	EDR	723	515	247	118	86	41	52	58	24	15	402
45–49	Act	6094	2125	662	245	148	93	60	45	38	20	9530
	A/E	19404%	13282%	6121%	2894%	2079%	1509%	1109%	904%	839%	487%	9627%
	EDR	751	524	251	125	95	74	58	50	49	28	424
50–54	Act	10,601	3703	1216	516	268	156	104	85	67	41	16,757
	A/E	12995%	8756%	4185%	2289%	1431%	983%	748%	683%	595%	405%	6500%
	EDR	747	514	256	148	98	72	58	56	51	34	428
55–59	Act	16,293	5522	1819	825	461	273	206	150	119	97	25,765
	A/E	8517%	5551%	2664%	1572%	1077%	774%	689%	573%	523%	485%	4378%
	EDR	762	508	252	156	113	86	81	70	68	66	444
60–64	Act	23,061	7284	2517	1133	700	417	297	235	208	154	36,006
	A/E	5778%	3546%	1796%	1063%	811%	580%	484%	436%	442%	381%	2970%
	EDR	807	503	261	160	128	95	83	78	86	76	466
65–69	Act	29,557	8728	3136	1511	866	613	417	324	253	232	45,637
	A/E	4058%	2347%	1225%	774%	550%	476%	388%	351%	320%	357%	2092%
	EDR	847	497	264	171	124	114	94	88	83	104	488
70–74	Act	32,954	8767	3177	1521	871	573	400	324	229	172	48,988
	A/E	2989%	1617%	876%	574%	424%	355%	307%	301%	258%	240%	1613%
	EDR	936	509	275	180	133	115	103	109	94	90	553
75–79	Act	29,155	6833	2536	1173	670	413	255	209	148	103	41,495
	A/E	2292%	1141%	663%	441%	343%	285%	228%	235%	214%	197%	1304%
	EDR	1064	527	304	200	156	132	101	115	105	96	655
80–84	Act	18,890	3606	1331	572	296	189	111	79	56	40	25,170
	A/E	1780%	805%	496%	329%	246%	223%	186%	178%	173%	174%	1087%
	EDR	1275	561	336	209	146	135	104	102	104	113	820
85+	Act	11,001	1632	606	220	112	58	34	15	16	9	13,703
	A/E	1307%	565%	402%	260%	220%	193%	171%	109%	154%	118%	914%
	EDR	1592	631	431	244	194	158	130	18	131	48	1124
Total Act		180,486	49,240	17,327	7833	4459	2812	1911	1492	1144	874	267,578
Total A/E		3155%	1881%	1036%	665%	503%	412%	353%	334%	312%	295%	1857%
Total EDR		920	515	274	170	125	102	86	83	77	73	536

SEER changed its coding system for surgery in 1998. We found enough commonality between codes used in 1988–1997 and 1998–2003 to categorize lung cancer surgery into the following: no cancer surgery, local surgery, partial lobectomy, lobectomy without node dissection, lobectomy with node dissection, pneumonectomy, radical pneumonectomy, extended radical pneumonectomy, distant surgery, and surgery not otherwise specified (NOS).

We used Stata's Kaplan-Meier survival function to obtain estimates for the 5- and 10-year survival percentages in Table 1. Separate analyses were performed for the entire population and for each characteristic in the tables, (ie, Age, Histology, AJCC, and Grade).[3]

For reference mortality, we used US Population mortality tables published by the CDC Division of Vital Statistics. We interpolated q_x values for those years with-

Table 3. Mortality Results by Histology Group and Duration

Histology		Duration										Total
		1	2	3	4	5	6	7	8	9	10	
Adenocarcinoma	Act	52,687	14,878	6373	3190	1925	1202	822	635	503	384	82,599
	A/E	2898%	1509%	917%	622%	491%	396%	339%	315%	303%	286%	1515%
	EDR	774	382	228	151	118	94	80	75	73	69	409
Large Cell	Act	12,154	2741	912	441	285	153	115	101	71	56	17,029
	A/E	3810%	2032%	1047%	701%	574%	388%	354%	377%	313%	295%	2145%
	EDR	1061	541	267	170	138	87	79	89	71	67	593
Other Epithelial	Act	46,204	8921	2929	1133	554	326	197	116	79	71	60,530
	A/E	3717%	2007%	1250%	820%	617%	548%	478%	373%	338%	415%	2607%
	EDR	1332	678	406	255	187	166	144	106	94	124	913
Small Cell	Act	31,295	10,339	2233	741	365	226	140	123	89	70	45,621
	A/E	4224%	4519%	2122%	1119%	750%	608%	467%	493%	443%	435%	3461%
	EDR	1035	1018	474	245	163	133	101	114	101	101	833
Squamous	Act	36,028	11,665	4605	2144	1224	825	571	454	354	260	58,130
	A/E	2419%	1563%	949%	624%	468%	406%	353%	341%	323%	295%	1445%
	EDR	771	472	277	176	129	112	98	98	94	85	458
Unknown	Act	2118	696	275	184	106	80	66	63	48	33	3669
	A/E	1930%	891%	420%	341%	232%	208%	197%	216%	191%	156%	733%
	EDR	405	167	69	53	31	26	26	32	26	16	147
Total Act		180,486	49,240	17,327	7833	4459	2812	1911	1492	1144	874	267,578
Total A/E		3155%	1881%	1036%	665%	503%	412%	353%	334%	312%	295%	1857%
Total EDR		920	515	274	170	125	102	86	83	77	73	536

Table 4. Mortality Results by AJCC Stage (Modified)

AJCC stage		Duration										Total
		1	2	3	4	5	6	7	8	9	10	
I	Act	13,408	8673	5105	3126	2108	1499	1063	894	708	528	37,112
	A/E	848%	733%	551%	432%	367%	326%	284%	284%	271%	246%	561%
	EDR	238	194	138	104	87	77	66	68	65	58	150
II	Act	2800	2121	1120	622	388	249	150	139	92	73	7754
	A/E	1202%	1349%	1000%	763%	628%	520%	392%	435%	349%	350%	956%
	EDR	293	320	234	176	144	120	86	103	80	82	231
IIIA	Act	14,617	7346	2642	1091	557	340	215	142	105	93	27,148
	A/E	2220%	2393%	1525%	1004%	722%	629%	542%	463%	432%	505%	1820%
	EDR	603	600	370	235	169	146	125	104	98	118	471
IIIB	Act	36,674	10,611	3118	1117	540	289	166	141	80	57	52,793
	A/E	3546%	3063%	1824%	1106%	810%	637%	490%	549%	399%	355%	2838%
	EDR	1043	773	442	261	189	147	112	133	92	81	779
IV	Act	96,324	14,648	3221	964	406	173	119	60	59	46	116,020
	A/E	6630%	4861%	2724%	1577%	1079%	694%	652%	418%	562%	583%	5668%
	EDR	1702	1144	642	375	258	164	160	99	140	150	1,433
Unstaged	Act	16,663	5841	2121	913	460	262	198	116	100	77	26,751
	A/E	2190%	1808%	1245%	899%	668%	519%	526%	392%	419%	431%	1689%
	EDR	863	676	445	304	216	162	164	114	131	133	637
Total Act		180,486	49,240	17,327	7833	4459	2812	1911	1492	1144	874	267,578
Total A/E		3155%	1881%	1036%	665%	503%	412%	353%	334%	312%	295%	1857%
Total EDR		920	515	274	170	125	102	86	83	77	73	536

Table 5. Mortality Observed During 11th Through 18th Durations, By AJCC Stage (85+ Age Band Experienced Only 14 Deaths)

Age		Modified AJCC Stage						Total
		I	II	IIIA	IIIB	IV	Unstaged	
40–44	Act	8	5	6	7	1	3	30
	A/E	283%	695%	864%	1476%	344%	1154%	569%
	EDR	10	37	42	82	16	66	26
45–49	Act	39	7	13	5	9	7	80
	A/E	425%	666%	861%	455%	1224%	561%	540%
	EDR	29	49	68	30	99	38	39
50–54	Act	91	25	13	22	10	15	176
	A/E	438%	602%	360%	784%	804%	978%	516%
	EDR	44	68	36	88	91	116	55
55–59	Act	155	25	28	26	6	19	259
	A/E	354%	440%	663%	627%	325%	738%	416%
	EDR	53	71	108	109	46	118	65
60–64	Act	272	35	43	39	8	31	428
	A/E	296%	326%	525%	591%	307%	654%	343%
	EDR	64	72	135	151	60	173	78
65–69	Act	335	45	29	24	16	28	477
	A/E	240%	349%	263%	350%	297%	353%	260%
	EDR	70	125	85	121	106	121	80
70–74	Act	290	33	25	20	5	29	402
	A/E	216%	330%	336%	222%	214%	304%	233%
	EDR	91	190	181	102	82	156	105
75–79	Act	165	16	9	10	4	16	220
	A/E	198%	271%	250%	237%	775%	241%	212%
	EDR	117	189	169	163	659	189	132
80–84	Act	53	5	4	1	3	9	75
	A/E	193%	240%	343%	32%	127%	291%	191%
	EDR	163	231	433	−133	49	353	162
Total Act		1408	196	170	154	62	157	2147
Total A/E		255%	368%	410%	402%	358%	418%	290%
Total EDR		64	89	93	101	81	125	74

out explicit mortality tables. In the case of 2005, we used 2004 q_x's.

Exposure-based mortality analysis was performed on the resulting dataset using a modified version of our previously described methodology.[4] In that article, we described using reference mortality based on life insurance experience. However, population mortality tables are created using exact ages, based on the individual's date of birth. We modified our procedures to estimate exact ages for exposures. SEER public-use data provides fields for year of birth, month and year of diagnosis, and age at diagnosis. From these 4 fields, we were able to estimate an approximate month for incrementing the subject's attained age, and exposure was tagged accordingly.

RESULTS

Table 1 displays the age, sex and other distributions for the study group. Note that the average follow-up time can be calculated by dividing the exposure by the count (N) of individuals in a given group. For example the overall average follow-up is 491,863.0 person-years/ 301,248 persons = 1.6 years.

Table 6. Mortality Observed During 11th Through 18th Durations, By Histology Type (85+ Age Band Experienced Only 14 Deaths)

Age		Adenocarcinoma	Large Cell	Other Epithelial	Small Cell	Squamous	Unknown	Total
				Histology				
40–44	Act	13	2	3	3	5	4	30
	A/E	559%	405%	2635%	811%	747%	308%	569%
	EDR	25	17	126	49	38	11	26
45–49	Act	33	11	9	7	15	5	80
	A/E	486%	723%	746%	1000%	678%	209%	540%
	EDR	34	58	60	76	53	9	39
50–54	Act	74	18	13	22	45	4	176
	A/E	468%	718%	627%	832%	631%	101%	516%
	EDR	47	82	74	94	75	0	55
55–59	Act	112	26	12	23	76	10	259
	A/E	389%	495%	436%	617%	462%	190%	416%
	EDR	58	85	68	95	81	18	65
60–64	Act	187	34	22	45	124	16	428
	A/E	310%	426%	408%	640%	347%	192%	343%
	EDR	67	102	96	171	83	28	78
65–69	Act	178	35	24	38	183	19	477
	A/E	217%	305%	268%	379%	324%	130%	260%
	EDR	57	101	87	134	118	15	80
70–74	Act	174	29	17	18	47	17	402
	A/E	223%	259%	193%	278%	259%	150%	233%
	EDR	96	127	74	126	130	36	105
75–79	Act	89	15	9	12	77	18	220
	A/E	166%	270%	171%	434%	295%	166%	212%
	EDR	77	210	89	354	235	81	132
80–84	Act	39	3	6	3	19	5	75
	A/E	197%	131%	226%	195%	280%	82%	191%
	EDR	171	49	213	171	317	−35	162
Total Act		899	173	115	171	691	98	2147
Total A/E		259%	358%	309%	485%	332%	153%	290%
Total EDR		61	91	82	123	103	17	74

Mortality results for the first 10 years by age band are shown in Table 2. Note the EDRs in excess of 1000 in several cells. Similarly, Tables 3 and 4 show the mortality results by histology and modified AJCC stage respectively.

There were 2161 deaths that occurred after the first 10 durations. Tables 5 and 6 summarize the mortality experienced in durations 11 through 18. The experience of 85+-year-olds is omitted from Tables 5 and 6 as there were only 14 deaths in that age band after duration 10.

DISCUSSION

It is no surprise that the mortality of lung cancer is very high, but when seen in a now familiar format it still amazes. In most studies, follow-up is limited by the end of study date and mean follow-up is close to one half the maximum follow-up. Although there are up to 18 durations of follow-up in this lung cancer dataset, the average follow-up time is only 1.6 years.

The ''unknown'' histologic category has a remarkably better survival rate than those

cases for which the histology is known. Some of the unknowns may actually be carcinoids or neuroendocrine tumors. Also, 43% of unknown histologies were Stage I.

One is accustomed to seeing excess deaths rates (EDR) of less than 100 deaths per thousand. In this instance, the EDR is greater than 1000 deaths per thousand. How can this be? The EDR is actually an annualized figure (deaths per thousand per year) and in lung cancer, a large fraction of patients die within the first year after diagnosis.

Although mortality results vary by histology and especially by stage, for even the best groups mortality is very high. Lung cancer is a common cancer and a substantial number of patients survive the first 10 years after diagnosis despite the 6.8% 10-year survival rate. Does this survival mean they have escaped the high mortality of lung cancer and can be considered standard risks?

Unfortunately, this is not the case. The overall mortality ratio for the 10th duration is 295% and for those surviving beyond 10 years (durations 11–18, see Tables 5–6) it is still 290%. Even Stage I tumors have a mortality ratio of 246% in the 10th duration and 255% after 10 years (Table 5).

REFERENCES

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