Research

"Blasts" from the Past: Lung Cancer in Cape Breton

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Abstract

Background: With the advent of molecular testing and its role in determining appropriate therapy for non small cell lung cancer (NSCLC), particularly adenocarcinoma, we reviewed charts from the Cape Breton Cancer Centre from 2011 to 2013, to determine availability of tissue for molecular testing. We were also interested in recording the distribution of histologic subtypes of NSCLC in this population.

Methods: A detailed chart review was carried out exploring relative rates of various histologies, smoking history, type of diagnostic procedure carried out, availability of tissue for further testing, and need for re-biopsy. When necessary for diagnostic clarification, pathology review was done.

Results: For convenience and to prevent selection bias, one hundred consecutive lung cancer cases coded as NSCLC by the provincial cancer registry were reviewed. The highest percentage was squamous cell (40%), followed by adenocarcinoma (29%), NSCLC not otherwise specified (18%), large cell (6%), neuroendocrine (4%), and adenosquamous (3%). These figures are out of line with typical North American figures and are similar to findings from the 1950s and 1960s.

Conclusion: This study demonstrated more than expected squamous cell NSCLC and less adenocarcinoma. Environmental and lifestyle issues may be implicated. With recent environmental changes and the enactment of an anti-smoking bylaw in Cape Breton, we expect to see these figures change to those more typical for North America.

In past studies by Health Canada, the Cape Breton region (Nova Scotia, Canada) demonstrated significantly higher cancer mortality in both men and women compared to the rest of Canada.[1] Because of this finding, there have been a variety of cancer control efforts in Cape Breton over the last two decades.

Lung cancer is the second most common cancer in both male and female Canadians, after prostate cancer and breast cancer, respectively.[2] In 2013, lung cancer represented 13.8% of new cancer cases in males and 13.3% of new cancer cases in females.[2] Non-small cell-lung cancer (NSCLC) makes up the majority of lung cancer cases in North America representing 85-90% of all lung cancers.[3] NSCLC is comprised of three main subtypes: adenocarcinoma, squamous cell carcinoma and large cell lung cancer. According to the American Cancer Society, adenocarcinoma represents the majority (40%) of the NSCLC subtypes.[3] This has not always been the case. Thirty years ago squamous cell histology was most common, but adenocarcinoma has surpassed squamous cell in the last 20 years.[4]

Treatment options for NSCLC have traditionally been quite limited. Surgery and radiation therapy for early-detected disease is associated with reasonable cure rates.[3] However, treatment of advanced disease is mainly limited to the use of modestly beneficial chemotherapy, but is associated with considerable toxicity.[3]

In order to improve outcomes in advanced NSCLC, systemic therapy must be improved. Traditional chemotherapy is somewhat limited in its ability to induce tumor regression and improve overall survival. Various molecular targets have been identified that can be exploited with newer targeted therapies.[5] These molecular targets have been primarily identified to be effective predictors of treatment response in adenocarcinoma but not in other histologic subtypes.[5] One example of this is epidermal growth factor receptor mutation (EGFR), or over-expression. Such a finding leads to improved response rate and improved overall survival when inhibitors of EGFR are employed.[6] A similar improvement in outcome has been observed when anaplastic lymphoma kinase (ALK) rearrangements are identified. This rearrangement

occurs in only 4% of patients with adenocarcinoma but its identification is important. ALK mutation patients can benefit from the targeted agent crizotinib with minimal toxicity.[6] A caveat, however, is that molecular testing can be expensive (often exceeding $1000 per panel of tests).[7]

We reviewed the charts of 100 consecutive patients referred to the Cape Breton Cancer Centre from 2011 to 2013. One hundred consecutive patients were picked for convenience, investigator time restrictions, and an attempt to eliminate selection bias. Our initial intent was to identify whether these patients had adequate tissue available to do molecular testing, and to determine the distributions of various sub-types of NSCLC in this patient population.

When looking at sub-types of NSCLC, our hypothesis was that we would find a distribution of tissue types similar to the rest of North America, i.e. adenocarcinoma as the most common type.

Methods

After our research protocol was approved by our local research ethics board (REB), a summer student was hired to review charts and pathology reports of 100 consecutive Cape Breton patients identified and referred to the Cape Breton Cancer Centre with a diagnosis of NSCLC. The Nova Scotia Cancer Registry was utilized for identification of these patients during the period 2011 to 2013. The charts of these 100 patients were reviewed in regards to various demographic characteristics, occupation, smoking history, stage at diagnosis, biopsy procedure, pathology, primary treatment and outcomes. Particular attention was paid to availability of tissue for molecular testing. When pathology reports gave an uncertain diagnosis, the tissue samples were reviewed with the reporting pathologist. Comparison between the observed proportions of adenocarcinomas and squamous cell carcinomas, and those reported previously in the literature was done by performing one-sample test of proportions, using the binomial approximation to the normal distribution. All tests were done in a two-tailed manner, with a 95% level of confidence.

Results

Table 1 is in keeping with Canadian Cancer Registry Data, in that NSCLC is more common in men and those with a heavy smoking history.[2] Our cohort however had a lower percentage of lung cancer patients who had never smoked (5%) compared to Canadian Data (15%). Stage at diagnosis is also in keeping with Canadian Cancer Registry data. The high number of patients alive at the time of review is in keeping with their recent diagnosis.

Gender	**Number of patients**
Male patients	55
Female patients	45
Smoking history	
Never smoked	5
< 10 pack years	12
> 10 pack years	80
Unknown	3
Survival status at time of review	
Alive	77
Deceased	23
Cancer stage	
I	28
II	11
III	34
IV	24
Unknown	3

Table 1. Demographics of 100 patient NSCLC cohort (2011-2013)

In North America, published literature reveals that adenocarcinoma makes up roughly 40% of all lung cancer.[3] Table 2 indicates that adenocarcinoma represented only 29% of all lung cancers. The observed proportion of adenocarcinomas is statistically different from the expected proportion of the same (P=0.03, 95% CI, 0.206 to 0.391).

Cancer diagnosis	**Number of patients**
Squamous cell	40
Adenocarcinoma	29
NOS	18
Large cell	6
Neuroendocrine	4
Adenosquamous	3
Total	100

Table 2. Pathologies of lung cancer patients from 100 patient cohort

Similarly in North America, literature shows that squamous cell carcinoma should make up roughly 25% of all lung cancers.[3] In our study, squamous cell carcinoma represented 40% of all lung cancers. The difference between the observed proportion and the expected proportion was statistically significant (P=0.001; 95% CI, 0.305 to 0.503).

Therefore, in this particular cohort (Cape Breton Island), squamous cell carcinoma is not only more prevalent than adenocarcinoma, but also more prevalent than the expected range of squamous cell carcinoma for the rest of the country.[2] Conversely, adenocarcinoma is far less prevalent than expected.

This is an unusual finding in Canada. However, similar irregularities have been identified in the United Kingdom in 2008 where squamous cell carcinoma was found to be more prevalent than adenocarcinoma.[8] This analysis was of patients diagnosed from 1995 to 2004 which is an earlier cohort than our study population. Within this United Kingdom cohort, the increased prevalence of squamous cell histology was associated with increased "social deprivation". Interestingly, in England smoking prevalence increased with socio-economic deprivation.[9]

Discussion

Lung cancer is the leading cause of cancer related deaths in Canada, accounting for 26.5% of all cancer-related mortalities in 2013.[2] Prior to the National Cancer Institute of Canada (NCI-C) study by Rapp and colleagues, published in 1988, the primary therapy for advanced NSCLC was radiation therapy and supportive care.[10] This NCI-C study demonstrated a modest survival benefit of approximately two to three months with platinum based chemotherapy versus best supportive care (BSC). Since this landmark paper, survival benefits with newer chemotherapy regimens has remained fairly static.[11]

More recently with the advent of newer targeted therapies, potentially more effective and less toxic treatment regimens are emerging.[5] Currently the most promising targets include the ALK-fusion protein, and both mutations and overexpression of EGFR.[12] When ALK-fusion protein is identified, treatment with the protein kinase inhibiter crizotinib has been associated with response rates of 65% as compared to 20% for standard chemotherapy.[13]

Studies of the use of EGFR inhibitors has also demonstrated that response rates in patients with unknown EGFR status is less than 10% while response rates in patients with known EGFR mutation or over expression is greater than 30%.[14] Interestingly, these targets are more often seen in adenocarcinomas than other histologies, particularly squamous cell histology.[15]

Given this set of circumstances, we felt that it was important to get a sense of the potential demand for molecular testing for the community of Cape Breton Island. We wanted to know the percentage of our NSCLC patients who had adenocarcinoma and therefore might benefit from further molecular testing.

As an aside, in a report by Yang Mao in 1983, Cape Breton was identified as having an excess of 19% for male cancer mortality and an excess of 13% for female cancer mortality when compared with the rest of Canada.[1] This disturbing figure has lead to various cancer control efforts in Cape Breton over the last 20 years.

Our study demonstrated an unexpected finding: Cape Breton had a signficiantly higher proportion of squamous cell histology than adenocarcinoma. Could

Tissue Type	Biopsy procedure	Number of patients
Cytology	Transthoracic FNA	61
	Pleurocentesis	1
Histology	Bronchoscopy	27
	Lobectomy	7
	Thoracoscopy	3
	VATS Wedge Resection	1
	Total number of biopsies	100

Table 3. Source of original diagnostic biopsy material at time of lung cancer diagnosis 100 patient NSCLC cohort (2011-2013)

Picture 1. Cape Breton Airshed circa 1970

Picture 2. View of Sydney Steel Plant from across Sydney Harbour

there be an easy explanation for the over-representation of squamous cell cancer in Cape Breton?

Squamous cell differentiation in NSCLC is felt to be more commonly seen in areas with a high particulate load in the ambient airshed and in heavy smokers.[16] Sydney, Cape Breton's largest city, was host to the Sydney Steel Plant throughout the 20th century. This plant was situated in the middle of the most densely populated area of the city. From the opening of the Sydney Steel Plant in 1901 until the shut down of the plant's blast furnace in 1988, there were over a million tons of particulate matter vented into the Sydney airshed.[17] Local residents vividly recall the bright orange sunsets and also having to clean iron ore resiude off their car windshields every morning (see picture 1 and 2).

A provincial report by Pierre Lavigne in 1997 revealed that Cape Bretoners had the highest rates of smoking in the province.[6] Our cohort demonstrated a lower percentage of "never smoked" then expected. These two points, i.e. increased particulate matter in the airshed and higher smoking rates, could explain the higher than expected squamous cell histology. Since 1988, there have been two major efforts that may ultimately decrease cancer incidence in Cape Breton, particularly squamous cell lung cancer. The first was converting from a blast furnace to make steel to an electric arc furnace in 1988. The second was the implementation of a very comprehensive public places anti-smoking bylaw in 2002.[18] These two measures have led to a marked improvement in the particulate matter in the Sydney airshed.[19]

In regards to the future, we do expect to see the relative rate of squamous cell histology to adenocarcinoma decrease. It's been 26 years since the closure of the Sydney Steel blast furnace and 13 years since the implementation of the Cape Breton anti-smoking bylaw. Typical latency period between exposure to a carcinogen and development of lung cancer is 30 years.[20] This prediction and its testing makes Cape Breton and particularly Sydney an ideal epidemiologic lab.

A follow-up to this study is planned in five years time. We expect to see the relative rates of squamous cell carcinoma to adenocarcinoma decrease. This would be more reflective of the rest of North America. But as of now our lung cancer situation continues to reflect the environment of Cape Breton until closure of the Sydney Steel Blast furnace: essentially, a 'blast' from the past.

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