

Current Diagnosis and Management of Cancer of Unknown Primary Site in Nova Scotia, Canada:

Basis for development of clinical practice guidelines

N. Power, B. Sabo, R. Dewar, M. Bullock, M. MacIntyre, A. Padmos, A. Casson

Cancer Care Nova Scotia and Dalhousie University, Halifax, Nova Scotia, Canada

Between 1992 and 1999, 1421 cases of cancer of unknown primary site (CUPS) were reported in Nova Scotia (1). The prognosis for this group of patients was very poor with a mean survival of 5.2 months. A retrospective study of the diagnostic workup, therapy, response to treatment, and survival for a randomly selected group of CUPS cases from four subsets was completed. The four subsets analyzed were: adenocarcinoma of varying degrees of differentiation, neoplasms not otherwise specified (NOS), poorly differentiated carcinoma or carcinoma not otherwise specified, and squamous cell carcinoma. Findings demonstrated variation in clinical practice. The data suggests that evidence-based and cost-effective guidelines should be developed to standardize diagnostic workup and best treatment options for patients presenting with CUPS. A standard provincial or national clinical practice guideline for patients with CUPS does not currently exist. The purpose of this paper is to present a Nova Scotian perspective on CUPS patient care to aid in the formation of a provincial and national, evidence based, and critically appraised practice guideline.

Corresponding Author: Box 77 Sir Charles Tupper Building, Halifax, NS, B3H 4H7, Canada, npower@tupmcm1.med.dal.ca

Introduction

Cancer of unknown primary site (CUPS) or occult primary tumors account for 3% to 10% of all new cancer diagnoses (2). The definition of CUPS varies within the literature and is largely dependent on the extent of diagnostic workup completed to classify the disease. Treatment in this group has historically had disappointing outcomes. These facts contribute to the nihilistic approach often extended to a CUPS patient (3).

Although local treatment with surgery and radiotherapy or a combination of both may be considered for the few patients who present with malignancy of a single site, most CUPS patients will require systemic therapy due to multi-organ involvement. Empiric therapy response has previously been poor with median survival from diagnosis usually less than 8 months (3).

However, a number of patient subsets comprising approximately 40% of all CUPS patients in reviewed literature respond favorably to treatment. The goal of diagnostic workup should be to rule out these specific subgroups (2). The subsets of patients with CUPS that responded favorably to treatment were: squamous cell carcinoma in cervical lymph nodes, women with peritoneal carcinomatosis, women with adenocarcinoma in axillary lymph nodes, poorly differentiated adenocarcinoma and carcinoma involving midline structures, poorly differentiated neuroendocrine tumors, and men with osteoblastic bone metastasis and/ or elevated PSA. If the diagnostic workup does not identify one of these subsets, limited treatment is available.

The outcome of a future standard clinical practice guideline for CUPS diagnostic workup should be to improve the health care provided to these patients. The guideline should be cost-effective, ethical, and enhance quality of life for the patients involved by recognizing when to curb invasive tests and when to start end of life management.

Methods

Retrospective Analysis of Cancer Registry Charts

Nova Scotia Cancer Registry patient files from January 1,

1992, through December 31, 1999 were retrieved to identify adult patients who presented with metastatic CUPS at the Nova Scotia Cancer Center, QEII Health Sciences Center, Halifax, Nova Scotia: a 1075-bed tertiary care center affiliated with Dalhousie University. Medical records were retrieved from the cancer registry by sex, age, method of diagnosis, CUPS diagnosis date, primary histology International Classification of Diseases (ICD) code, county in Nova Scotia patients initially presented in, and death date if patient died. This search resulted in the retrieval of a total of 1421 medical records. Survival curves were constructed using Kaplan and Meier analysis. Statistical significance was calculated by the log rank test.

A categorical breakdown of the primary histologic findings identified four major types of cancer associated with a CUPS diagnosis (Table 1):

- adenocarcinoma of varying differentiations (34.9%)
- neoplasms not otherwise specified (33.6%)
- poorly differentiated carcinoma or carcinoma not otherwise specified (NOS) (18.16%)
- squamous cell carcinoma (5.7%)

Two random cohorts for each of the types of cancer were assigned: (a) diagnosis date between January 1, 1992 through December 31, 1995, and (b) diagnosis date between January 1, 1996 through December 31, 1999. Ten random charts from each of the four major categories as well as for each cohort yielded a total of 80 charts. Four charts were unable to be located due to clerical errors. Improperly labeled ICD codes yielded twenty charts of adenocarcinomas with varying degrees of differentiation, thirteen charts of neoplasms not otherwise specified, twenty-six charts of poorly differentiated carcinomas and carcinomas not otherwise specified, and seventeen charts of squamous cell carcinoma. The resultant study population consisted of 32 females (mean age 67.1, median age 65) and 44 males (mean age 63.2, median age 66).

A total of 76 charts were reviewed for presenting site of metastasis, type of biopsy and results, diagnostic tests ordered and results, treatment details, follow-up results, and palliative therapy given (Figure 1).

Cohort A: 01/01/92-12/31/95 Cohort B: 01/01/96-12/31/99

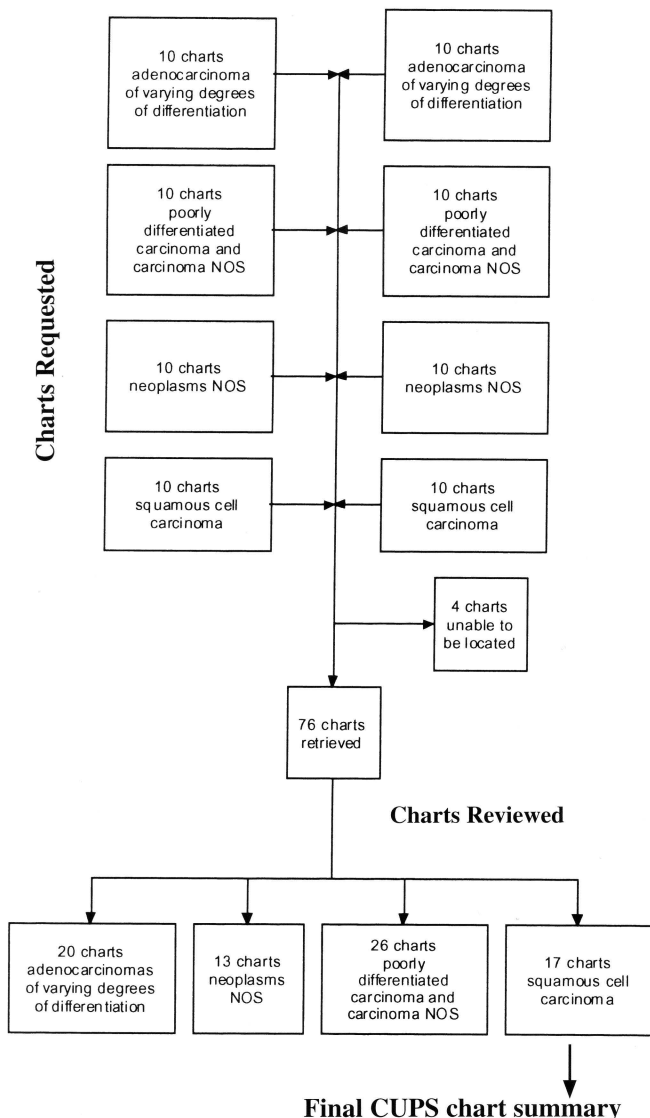


Figure 1. Selection of charts for review.

Results

Figure 2 demonstrates that Nova Scotia has a greater percentage of CUPS (as compared to all cancer reported) than any other province or territory in Canada.

Victoria and Cumberland counties have the highest rates of CUPS in the province (figure 3). Notable other counties are Cape Breton (19.9 per 10 000) that has the highest cancer rate incidence in all of Canada (5) and Halifax (13.8 per 10 000) that has the Nova Scotia Cancer Centre and the highest concentration of cancer care specialists and medical equipment in the province.

Table 1 summarizes the results of the 1421 Nova Scotia Registry patients' histology. The top 4 histological subtypes and the percentages recorded in table 2 are as follows: adenocarcinoma comprised 55.7% of cancer patients, poorly differentiated/ undifferentiated carcinoma 34%, malignant neoplasm NOS 1.8%, and squamous cell carcinoma 8.4%.

The primary presenting sites of the 76 patient in the retrospective study were head and neck (17 patients), bone (14 patients), and brain (9 patients), summarized in table 3. Physical symptoms from the study (table 4) were dominated by musculoskeletal problems (32 patients) and head and neck symptoms (16 patients). The diagnostic tests ordered varied greatly with each of the 76 patients as illustrated in table 5. Figure 4 summarizes the treatment approach for the 76 patients. Radiation therapy alone (32.9%) and supportive measures only (31.6%) were the most likely treatment options started.

Overall survival for the 1421 (CR) cancer registry CUPS patients was 5.6 months compared to the 76 patient (RS) retrospective study survival of 6.1 months. Specific histology subtype survival for each of these patient populations from figures 5 and 6 were: adenocarcinoma (CR= 11.1 months, RS= 5.6 months); squamous cell carcinoma (CR= 16.2 months, RS= 13.9 months); poorly differentiated carcinoma (CR= 9.8 months, RS= 5.8 months); and neoplasm not otherwise specified (CR= 4.0 months, RS= 3.6 months).

Discussion

CUPS results from an occult cancer that produces clinically significant and documented metastases. The etiology varies considerably depending on the malignant organ of origin. In a minority of patients, the primary site is not even apparent at autopsy. For example, one large series reported on 302 patients with CUPS found that in 16% of patients, the primary

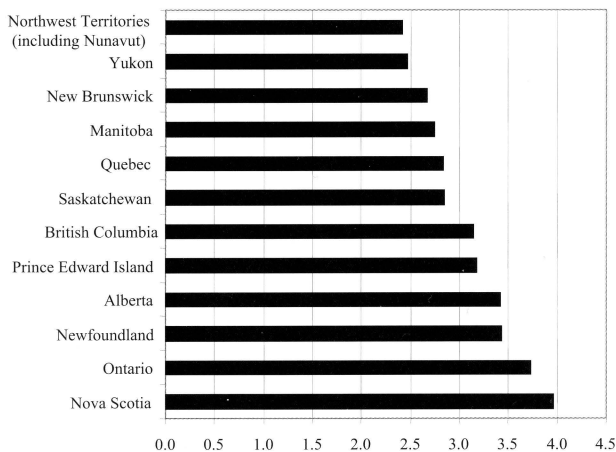


Figure 2. Provincial Variation in Cancer of Unknown Primary as a % of all Cancer Reported in Canada⁵.

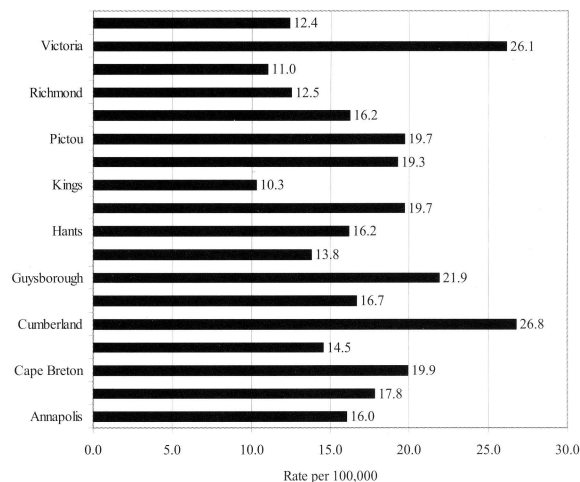


Figure 3. Nova Scotia Cancer of Unknown Primary Rates by Nova Scotia County 1994-1999 per 100, 000⁵.

Category	Percentage
Adenocarcinoma	34.90%
Squamous Cell Carcinoma	5.56%
PD Carcinoma or Carcinoma NOS	18.16%
Neuroendocrine	1.55%
Thyroid	0.00%
Neoplasm, NOS	33.57%
Carcinoid	0.70%
Melanoma	1.83%
Sarcoma	0.14%
Histiocytoma	0.42%
Germinoma	0.07%
Neuroblastoma, NOS	0.07%
Neurilemoma, NOS	0.07%
Plasmacytoma, NOS	0.07%
Mastocytoma, NOS	0.07%
Page't's	0.07%

Table 1. Categorical Breakdown of all 1421 Nova Scotia Registry Patients with CUPS from 1992-1999.

Body Site	Number
Brain	9
Bone	14
Lung	5
Liver	9
GI Tract	2
Inguinal nodes	1
Axillary Nodes	1
Supraclavicular Nodes	5
Mediastinum	2
Malignant Pleural Effusion	2
Peritoneal	2
Retroperitoneal	2
Testicles	1
Breast	1
Head and Neck	17
Skin	1
None stated	2

Table 3. 76 Patient Retrospective Study Presenting Sites.

Category	Percentage
Adenocarcinoma	55.7%
Squamous Cell Carcinoma	34%
PD Carcinoma or Carcinoma NOS	1.8%
Neoplasm, NOS	8.4%

Table 2. Top Four Histological Subtypes of CUPS Patients.

System	Number
HEENT	16
MSK	32
Resp	6
CV	0
GU	1
GI	3
Endocrine	0
Neuro	10
none stated	8

Table 4. 76 Patient Retrospective Study Physical Symptoms by System.

neoplasm remained unknown even after autopsy. In CUPS cases at the QEII Health Sciences Center, the rate of occult cancer after autopsy may be as high as 70 to 80% (5).

Nova Scotia has the highest incidence of CUPS in Canada (5). This correlates with Nova Scotia's high incidence of all types of cancer. In terms of county differences within Nova Scotia, Cumberland and Victoria counties are the highest which may be due to a number of factors including patient lifestyle in a rural setting and more limited access to the provincial cancer centers located in Sydney (Cape Breton) and Halifax. Both Cape Breton and Halifax counties have comparable incidence rates to the rest of the province. This may discredit the hypothesis that access to more diagnostic capabilities results in identifying a primary cancer more frequently.

The 76 patient retrospective study presenting sites are summarized in table 3. Involvement of head and neck, various lymph nodes, bone, liver, and brain were most common but

other sites encountered were lung, testes, breast, peritoneum, gastrointestinal tract, mediastinum, skin and malignant pleural effusion. From table 4, the physical symptoms were dominated by musculoskeletal, head/ears/eyes/nose/throat, and neurological symptoms with respiratory, gastrointestinal, and genitourinary symptoms less common. The reason for these results may be explained by the signs and symptoms relating to the more common routes of metastases in other cancers.

When initial limited clinical screening does not reveal a potential primary site, a vast array of diagnostic tests is available. The diagnostic strategy must balance the fact that most patients have a poor prognosis, and therefore time-consuming, invasive, and expensive testing should be limited, with the need to identify treatable subsets quickly. Table 5 describes the diagnostic tests ordered in the seventy-six patient cases of the retrospective study, all of which were negative in their attempt to localize the primary site of malignancy.

Diagnostic Test	Number
Complete History	76
Physical Exam	76
Positive Family History	15
Chest x-ray	64
Urinalysis	6
Hemoccult Fecal Blood Test	2
Biopsy	63
Chest CT	39
Abdominal CT	24
Pelvic CT	16
Bone Scan	24
Examination Under Anaesthesia	17
Ultrasound	34
Head CT	33
Mammogram	13
MRI	8
Panendoscopy	17
Colonoscopy	6
Pleurodesis	0
Other Diagnostic Tests	58

Table 5. 76 Patient Retrospective Study Diagnostic Tests Ordered.

These results suggest that diagnostic procedures should be conservative and efficient; a careful history should be taken and a complete physical exam should be performed along with routine laboratory evaluation, a chest x-ray, and hemoccult fecal blood tests. These limited procedures are justified because they are low cost, non time consuming and have a high yield to rule out any obvious malignancies. Additional procedures (i.e. radiologic imaging and/or endoscopic examinations) are warranted only to evaluate specific presenting signs or symptoms as well as gender specific tests (i.e. PSA for males older than 40 years old if clinically relevant and mammography for females with clinical features suggestive of metastatic breast cancer). The diagnostic yield of other additional procedures is low and can add considerable expense and time to the initial evaluation. Extensive radiologic or endoscopic investigations of asymptomatic areas are rarely useful in identifying a primary site.

Treatment options for CUPS patients varied greatly and involved a number of combinations of chemotherapy, radiotherapy, surgery, and supportive therapy. The decision for one treatment over another was based on the clinical picture and the patient's wishes. The lack of randomly controlled trials in the treatment options contributed to such wide variation in practice.

The diagnostic tests completed were equally random and showed the greatest need for a clinical practice guideline. Due to the study population selected, patients who had a number of diagnostic procedures and finally found the primary cancer were excluded. This selection bias should be kept in mind when the guidelines are developed.

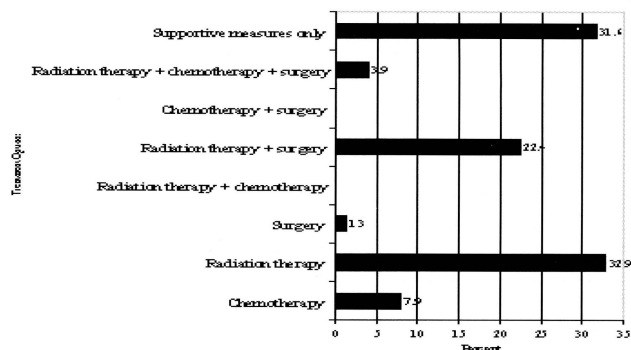


Figure 4. 76 Patient Retrospective Study Treatment Options Initiated (5).

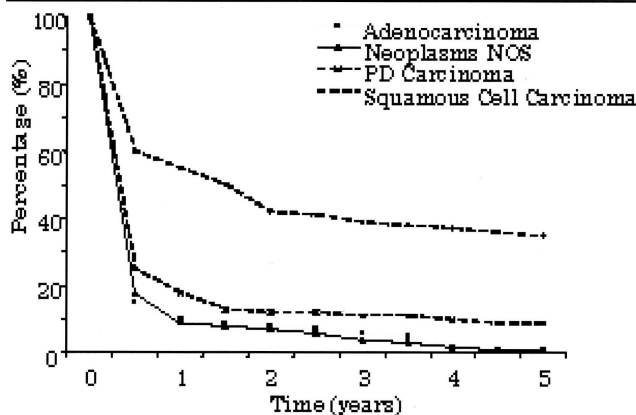


Figure 5. Survival Curve for all 1421 Nova Scotia Registry Patients according to histological classification.

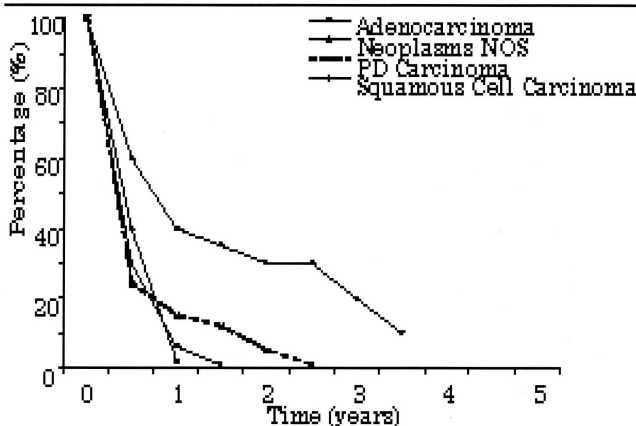


Figure 6. Survival Curve for 76 Retrospective Study patients according to histological classification.

Despite variation in diagnostic procedures and treatment, the survival of this patient population was still considerably low (see figure 5 and 6). Squamous cell carcinoma showed favorable survival due probably to the fact that it is usually confined to the head and neck area and treatment is more beneficial to a patient in this subset, with a combination of radiotherapy and surgery. Overall, survival for CUPS patients is significantly lower than most all other types of cancer. This fact illustrates two points succinctly: (a) there is a need for a clinical practice guideline to exclude unnecessary tests on patients near their end of life, and (b) randomly controlled trials are needed to optimize the best treatment strategies. Ultimately, supportive therapy may be the only appropriate treatment option.

Conclusion

The retrospective study of patients presenting with CUPS and the data analyzed from the Nova Scotia Cancer Registry suggests that a clinical practice guideline is needed in order to avoid unnecessary diagnostic tests and maximize health-care for these patients. When patients have been screened for primary sites that have more favorable outcomes, management recommendations need to be available for the cancer treatment team. The survival in this patient population despite the myriad of tests and various treatment options is unfortunately low. Therefore until new chemotherapy or better treatment options become available, conservative measures are suggested by these results.

Acknowledgement

Nicholas Power would like to thank Cancer Care Nova Scotia for the summer studentship grant as well as Dr Alan Casson and Brenda Sabo for their invaluable insight and advice into this important oncological entity. Also, the contributions from Dr Dewar, Dr MacIntyre, Dr Padmos, and Dr Bullock lent essential multidisciplinary expertise to the project.

References

1. The Canadian Association of Provincial Cancer Agencies (CAPCA) www.capca.ca, Nova Scotia Division.1. The Canadian Association of Provincial Cancer Agencies (CAPCA)
2. National Comprehensive Cancer Network: NCCN practice guidelines for occult primary tumors. Oncology (Huntingt) 1998 Nov;12(11A):226-309
3. Hainsworth JD, Greco FA: Treatment of patients with cancer of an unknown primary site. N Engl J Med 1993 Jul 22;329(4):257-63
4. Power N, Sabo B, Dewar R, Bullock M, MacIntyre M, Padmos A, Casson AG: Current Diagnosis and Management of Primary of Unknown Origin in Nova Scotia, Canada: basis for development of clinical practice guidelines. International Journal of Cancer 2002 Jul; 100(S13): 235.
5. Health Canada Population and Public Health Branch (PPHB): www.hc-sc.gc.ca/pphb-dgspsp/new_e.html.
6. Surveillance and Risk Assessment Division CCDPC-PPHB: Cancer Surveillance: http://cythera.ic.gc.ca/dsol/cancer/index_e.html.
7. Diggs CH. Cancer of unknown primary site. Deciding how far to carry evaluation. Postgrad Med 1989 Aug;86(2):186-91.
8. Abbruzzese JL, Abbruzzese MC, Hess KR, Raber MN, Lenzi R, Frost P Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. J Clin Oncol 1994 Jun;12(6): 1272-80.

About the Author

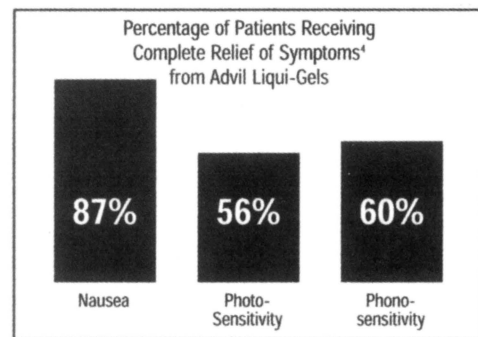
Nicholas Power is currently a third year medical student at Dalhousie University. He completed his undergraduate General Science degree at the University of New Brunswick in Fredericton, NB and the University of Bristol in Bristol, England. This Cancer of Unknown Primary project was presented at the 18th International Union Against Cancer Congress, Oslo, Norway by Dr Alan Casson on June 30- July 5, 2002. His plans for the future include applying to a Urological Surgery program in Canada and continuing research into oncological therapeutics.



Fast First Line Therapy
for mild to moderate
migraine symptoms^{1,2}

Advil[®]
Liqui-Gels[®]

- In addition to migraine pain, clinically proven to relieve nausea, photosensitivity and phonosensitivity³



- Twice as likely as acetaminophen to abort migraine within 2 hours⁴
- Acute pain relief comparable to prescription naproxen¹



References:

1. Data on file, Medical Department, Whitehall-Robbins Healthcare.
2. Packman EW, Doyle G, Koronkiewicz K, et al: Onset of analgesia of ibuprofen liqigels (400 mg) compared to acetaminophen caplets (1000 mg) in the treatment of tension headache. J Clin Pharmacol 1998; 38:842-86.
3. Kellstein DE, Lipton RB, Geetha R, et al: Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, doubleblind, placebo-controlled, dose-ranging study. Cephalgia 2000; 20:233-243.
4. Hamalainen ML, Hoppu K, Valkela E, et al: Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. Neurology 1997; 48(1):103-107.

* Liqui-Gels[®] is a registered trademark of R.P. Scherer International Corporation

Liquid-Fast Migraine Relief