Metastatic Patterns of Cancers

Results From a Large Autopsy Study

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● **Context.**—Many studies have addressed metastatic patterns seen among various cancers. No recent studies, however, provide quantitative analyses of such patterns arising from a broad range of cancers based primarily on postmortem tissue analyses.

Objective.—To provide a quantitative description of metastatic patterns among different primary cancers based on data obtained from a large, focused autopsy study.

Design.—Review of data from 3827 autopsies, performed between 1914 and 1943 on patients from 5 affiliated medical centers, comprising 41 different primary cancers and 30 different metastatic sites.

Results.—Testicular cancers were most likely to metastasize (5.8 metastases per primary cancer), whereas duodenal cancers were least likely to do so (0.6 metastases per primary cancer). Preferred metastatic sites varied among the primary cancers analyzed. Overall, regional lymph nodes were the most common metastatic target (20.6% of total), whereas testes were the least common (0.1% of total).

Conclusions.—Not surprisingly, different primary cancers tended to metastasize, with differing frequencies, to different sites. These varying metastatic patterns might be helpful in deducing the origins of cancers whose primary sites are unclear at presentation.

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Malignant neoplasms are, by definition, those that metastasize. By involving anatomic structures distant from the primary site and potentially disrupting their function, tumor metastases add to disease morbidity and mortality; hence, metastases from a known primary cancer will have dramatic effects on disease staging, prognosis, and treatment.[1] Additionally, cancers that present initially as metastases distant from their sites of origin (or cancer from unknown primary site) often require extensive investigation to determine their primary source to optimize treatment. In either scenario, whether cancer is tracked prospectively (from a known primary) or retrospectively (from an unknown primary), detailed observational templates that highlight expected metastatic patterns would be of great clinical benefit in both diagnosis and treatment.

By facilitating thorough postmortem examination of all tissues within the body, large-scale autopsy studies offer a powerful approach toward developing such templates. Perhaps owing to the general decline in hospital-based autopsies,[2–4] however, few such general studies are available in the current literature. Most contemporary autopsy studies focus on one specific type of primary cancer or site of metastasis but fail to address the broad spectrum of metastatic behaviors likely to be encountered in a clinical setting.[5,6] Other studies that do address this broad spectrum do not use postmortem tissue analysis as a primary source.[7] Indeed, we have found only one other autopsy study, published in 1950, that is of sufficient scope to address this broad spectrum.[8] Although data from more recent studies using such sophisticated technologies as whole-body magnetic resonance imaging,[9] positron emission tomography,[10] and computed tomography[11] have unquestionably contributed to the current understanding of metastatic disease, actual postmortem histologic analysis arguably remains the gold standard in the study of many disease processes,[12–14] including cancer metastasis. In the present study, we were fortunate to have access to a large archival collection of carefully documented postmortem histologic data on primary malignancies and metastatic sites.

MATERIALS AND METHODS

Archival data were examined from 4012 autopsies that included examination of all organ systems, performed on 2108 male and 1904 female patients between 1914 and 1943 at Harvard (Boston, Mass), Huntington (Huntington, Mass), Palmer (Palmer, Mass), Pondville (Walpole, Mass), and Westfield (Westfield, Mass) medical centers. None of these patients received chemotherapy or radiation treatment. Each autopsy fell into 1 of 46 different primary neoplasm categories (cases involving leukemia, endothelioma, lymphoma, and neuroblastoma were not included). The number of male versus female cases for each primary malignancy was not recorded; therefore, relative proportions of primary malignancies and metastases were calculated among all patients (male and female). Metastatic lesions generated by all neoplasms were quantified among 32 different anatomic sites, with the number of metastases generated from all primary neoplasms at a given site noted. The total number of metastases was 10 062. All primary neoplasms and metastases were analyzed by gross ex-

METASTATIC SITE

Figure 1 data table. Rows = PRIMARY NEOPLASM, columns = metastatic site.

Primary	n	Adrenal	Bone	Bladder	Brain	Breast	Diaphragm	Gallbladder	Heart	Kidney	Lung	Large intestine	Liver	Lymph nodes (reg)	Lymph nodes (dist)	Omentum	Ovaries	Pancreas	Pericardium	Peritoneum	Pleura	Prostate	Skeletal muscle	Skin	Small intestine	Spleen	Stomach	Testes	Thyroid	Uterus	Vagina	Σ
Adrenal	6	1	3	0	2	0	1	0	0	0	1	2	1	3	3	4	0	1	1	0	0	1	0	0	3	0	2	1	0	1	0	0	31
Anus	29	3	4	1	1	0	1	2	2	2	8	1	7	5	7	1	0	1	2	2	4	0	0	2	1	3	0	0	1	0	0	61
Appendix	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	4
Bile duct	34	3	3	0	0	0	0	2	0	0	4	1	10	15	2	0	0	1	0	5	2	0	0	0	0	2	1	0	0	0	0	0	51
Bladder	183	11	20	0	0	0	2	0	2	9	30	1	25	80	45	1	2	2	1	7	4	3	2	1	4	3	0	0	1	0	0	256
Bone	35	4	15	1	1	0	3	0	2	2	18	1	6	8	8	0	1	3	0	1	6	1	0	6	0	1	0	0	0	0	0	88
Branchial cyst	10	0	1	0	0	0	0	0	0	1	1	3	0	2	9	4	0	0	0	0	0	1	0	0	0	0	0	0	2	0	0	34
Breast	432	149	213	17	42	54	36	19	22	40	247	11	218	230	277	8	53	49	52	59	158	1	0	124	12	52	17	0	35	33	7	2235
Cervix	418	23	36	10	1	0	10	3	7	19	94	11	97	232	133	8	24	6	2	37	11	0	0	5	12	13	2	0	2	1	7	806
Colon	123	9	2	0	1	0	2	2	0	7	15	4	35	42	19	6	3	9	0	20	1	0	0	1	3	1	1	0	3	4	0	190
Duodenum	11	0	0	0	1	0	0	0	0	0	0	2	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7
Esophagus	129	6	6	0	0	0	2	0	3	4	19	1	21	70	22	0	0	4	3	4	8	0	1	2	1	2	2	0	2	0	0	183
Eye	10	3	1	0	1	0	0	1	4	1	4	0	6	0	3	0	0	2	0	1	2	0	0	2	1	0	0	1	0	1	0	34
Gallbladder	35	5	3	1	0	0	3	1	0	1	9	2	18	21	13	3	0	8	0	4	2	0	0	2	3	2	1	0	0	0	0	102
Kidney	62	18	20	2	4	1	2	1	8	8	30	5	21	23	26	1	1	9	1	6	10	1	1	3	4	3	2	0	1	0	0	212
Larynx	82	2	4	0	0	0	1	1	0	2	13	0	5	31	11	0	0	0	0	0	3	0	0	1	0	0	0	0	2	0	0	76
Lip	45	0	1	0	0	0	0	0	0	1	0	4	0	1	27	6	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	41
Liver	36	7	3	0	1	0	3	1	2	0	16	1	0	18	8	2	0	4	0	7	3	0	0	1	1	0	0	1	1	0	0	80
Lung	163	59	38	1	15	0	12	6	17	30	48	9	58	114	76	4	0	23	13	12	27	1	2	8	6	18	5	0	15	1	1	619
Ovary	86	9	6	6	2	0	13	2	2	8	18	7	25	36	26	12	6	2	2	63	16	0	0	4	6	8	4	0	2	11	6	302
Pancreas	109	12	7	2	0	1	13	4	1	8	29	4	63	68	35	7	4	0	2	25	11	1	0	3	6	7	4	1	3	2	0	323
Penis	19	2	1	1	0	0	0	0	4	0	5	0	0	11	4	0	0	0	0	1	1	1	0	3	0	0	0	0	0	0	0	34
Pharynx	117	1	7	0	2	0	1	1	1	1	15	0	23	60	20	1	0	0	0	0	2	0	0	1	1	2	0	0	6	0	0	145
Pleura	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Prostate	193	16	91	5	0	0	1	4	1	8	59	1	36	121	85	0	0	6	0	2	8	0	0	2	1	8	1	4	2	0	0	462
Rectum	437	33	27	10	2	0	5	5	4	13	86	4	120	167	90	3	10	4	2	25	11	8	2	8	3	8	0	0	8	8	3	669
Retroperitoneum	10	1	1	2	0	0	1	0	0	2	3	2	3	4	3	2	0	2	0	2	0	2	1	0	1	1	2	1	1	0	0	37
Salivary	8	1	2	0	1	0	0	0	0	1	2	1	2	4	0	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	17
Skin (body)	67	19	18	2	10	2	7	4	11	13	34	2	20	34	31	1	2	11	8	8	11	2	3	16	9	11	5	2	13	2	1	312
Skin (lower face)	21	2	2	0	0	1	1	2	1	2	5	0	3	8	6	1	1	1	0	2	1	0	0	2	0	0	0	0	0	1	0	42
Skin (upper face)	73	4	5	0	5	0	0	1	2	3	8	1	5	10	8	0	1	2	0	1	0	1	0	4	2	1	0	0	1	1	0	66
Small intestine	19	0	0	0	1	0	1	1	0	0	3	2	8	6	1	1	1	0	0	5	1	0	0	0	1	1	1	0	0	0	0	34
Stomach	348	39	33	7	1	2	18	20	8	10	65	12	125	225	104	28	28	40	3	79	15	4	1	9	24	13	1	0	3	11	0	928
Testis	25	6	8	0	1	0	3	1	2	11	18	2	19	19	21	3	0	3	4	6	3	1	2	2	3	3	2	1	2	0	0	166
Thyroid	43	4	6	0	1	0	0	0	3	1	22	0	10	19	13	0	0	3	4	0	5	0	0	4	1	0	0	0	0	0	0	96
Tongue	165	5	7	0	0	0	2	0	8	6	19	0	8	107	33	0	0	2	0	4	8	0	0	2	2	4	0	0	1	0	0	218
Tonsil	36	2	3	0	0	0	1	0	0	1	6	0	6	24	9	1	0	1	0	1	3	0	0	1	0	27	0	0	0	0	0	86
Unknown primary	44	6	10	1	4	0	1	0	1	5	16	4	2	9	18	2	4	8	2	3	6	1	1	4	1	2	1	1	4	1	0	118
Uterus	120	14	8	5	0	1	2	2	1	8	30	2	34	64	42	6	15	4	0	20	7	0	0	4	5	1	2	0	5	0	7	289
Vagina	11	2	1	0	0	0	0	0	2	0	3	1	3	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	16
Vulva	30	0	1	1	0	0	1	0	2	0	6	0	2	18	6	0	0	0	1	0	2	0	0	2	0	1	0	0	0	0	0	43
Σ= 3827		482	617	75	100	62	149	86	125	228	1018	94	1051	1946	1224	102	158	212	102	413	355	28	16	233	114	201	55	12	117	77	32	Σ= 9484

Figure 1. *Data table for analyzed cases (for description, see "Results").*

amination and on histologic sections. After review of these orig-inal data, 2 primary neoplasm categories were excluded from the final analysis because of ambiguity in the record. Three other primary neoplasm categories (mediastinum, lymph node, and brain) were also excluded because of insufficient numbers of events. Our final data set includes 3827 autopsies (41 primary neoplasms) and 9484 metastases (30 metastatic sites).

RESULTS

Figure 1 shows the distribution of the 3827 autopsies by primary malignancy (y-axis) and metastatic site (x-axis), each listed in alphabetic order. Listed in blue are individ-ual numbers of each primary neoplasm. As shown by the blue bars in Figure 2, the most common primary cancers
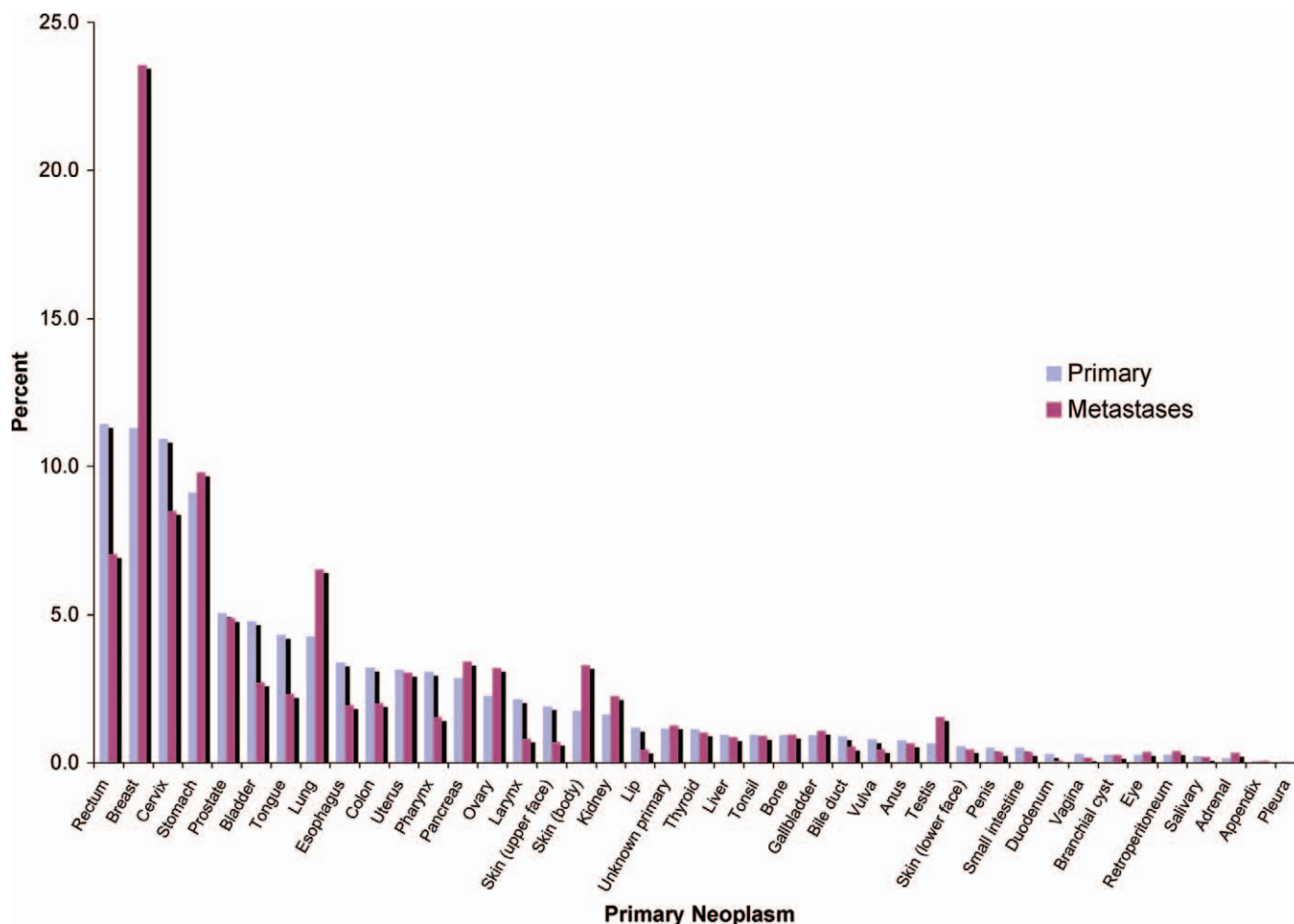
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Figure 2. For each primary neoplasm, the relative proportion of malignancies (blue bars) and of the metastases generated by them (red bars) as a percent of the total.

were, in descending order, rectum (11.4%), breast (11.3%), cervix (10.9%), stomach (9.1%), and prostate (5%). Also shown in Figure 1 is the distribution of the 9484 metastases generated by the 3827 primary neoplasms among 30 different anatomic sites (numbers in green). The total contribution from each primary malignancy to all metastatic sites is listed in red numbers. The red bars in Figure 2 illustrate the relative proportion of metastases that each primary malignancy contributed to the final metastatic pool. Comparing corresponding red and blue bars indicates that some primary malignancies, including breast, lung, kidney, and testes, generated a disproportionate number of metastases, relative to their representation within the total pool of primary cancers (see also Figure 4, A).

Metastasis to each site, in decreasing frequency, is shown in Figure 3. Consistent with their putative function as primary mechanical barriers against many metastatic cancers,[15] local and regional lymph nodes were the most frequent metastatic targets (20.5% and 12.9%, respectively). Liver, lung, and bone were the next most common metastatic targets, with 11.1%, 10.7%, and 6.5%, respectively, of all primary malignancies targeting these sites of high vascular flow. Indeed, most of the different primary neoplasms listed in Figure 1 metastasized, at varying frequencies, to these common sites. Conversely, the 5 least common metastatic sites are shown in order of decreasing

frequency in Figure 3: stomach (0.6% of metastases), vagina (0.3% of metastases), prostate (0.3% of metastases), skeletal muscle (0.2% if metastases), and testes (0.1% of metastases).

The tendency for certain cancers to metastasize more readily than others is illustrated in Figure 4, A, which shows the average number of metastases per primary neoplasm. For each type of malignancy, values were derived by dividing the total number of metastases (Figure 1, numbers in red) by the total number of primary neoplasms (Figure 1, numbers in blue). Figure 4, B, depicts the distribution of the metastases among all 30 metastatic sites by the 10 malignancies that generated the highest average number of metastases per primary neoplasm (testes, breast, adrenal, skin, lung, retroperitoneum, ovary, kidney, eye, and pancreas). Breast cancer (in yellow) contributed the greatest proportion of metastases to the broadest range of sites.

Figure 5 depicts the frequencies at which all primary malignancies were distributed among the 5 most and least common metastatic sites (see also Figure 3). As previously noted, most primary malignancies metastasized to varying degrees among regional lymph nodes (38 primaries of 41 analyzed). Of these primary malignancies, cervical cancer was the most common and appendix was the least common, seen in 11.9% and 0.1%, respectively, of all metastases to regional lymph nodes. Conversely, the least
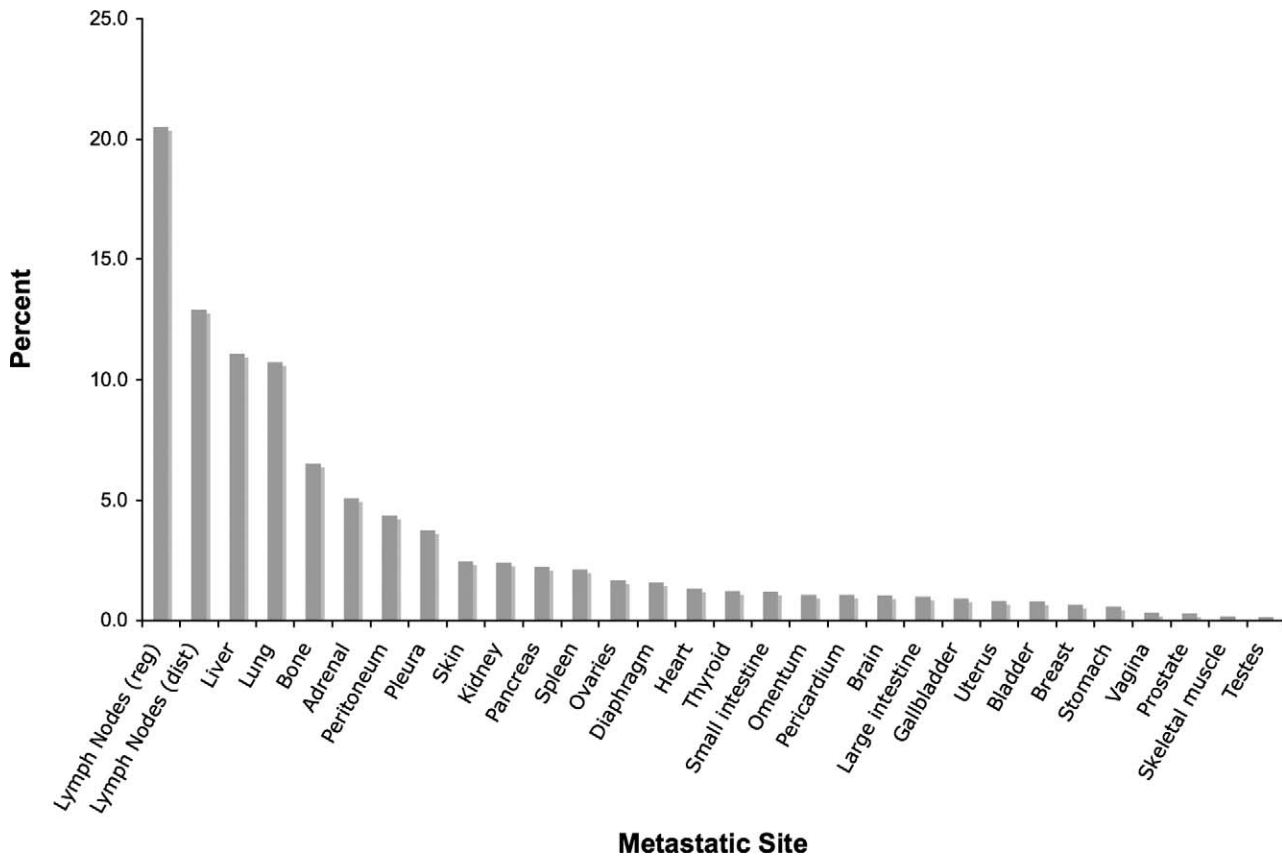
Figure 3. *Relative proportions of metastases by site (as a percent of the total).*

common metastatic site, testes, was targeted by only 9 primary malignancies. Of these testicular metastases, those from prostate were found most commonly (33% of metastases), and unknown primaries were found least commonly (8.3% of metastases).

COMMENT

Findings from this study provide a comprehensive overview of metastatic behaviors as seen among both common and uncommon cancers during the 29-year period in which they were collected. As actual postmortem tissue analyses from the largest cohort of autopsies reported to date in the medical literature, these findings provide a sensitive, quantitative baseline of metastatic patterns seen among the analyzed malignancies. Figures 1 through 5 illustrate the utility of such a baseline, whether following potential metastases from a known primary malignancy or predicting the origin of an unknown primary malignancy by its metastatic behavior. For a given neoplasm, Figures 1 and 2 show its representation and relative propensity to metastasize, and Figure 4, A, shows its absolute propensity to metastasize. For a given metastatic site, Figure 3 shows the frequency at which that site was targeted, whereas Figure 4, B, shows the representation of each of the 10 most highly metastasizing primary malignancies at that site. Finally, Figure 5 highlights the representation of all primary malignancies among the most and least common metastatic targets. Our hope is that such an integrated picture will not only contribute to the general knowledge base of cancer behavior but also facilitate the development of testable hypotheses that drive more tar-

geted studies on these clinical phenomena and their underlying mechanisms.

A comparison between the findings of this study and those reported in the 2006 National Center for Health Statistics report reveals marked decreases in deaths attributed to some cancers. Stomach cancer, which represented 9.1% of our cases, currently accounts for only 2% of cancer deaths. Another striking example is cervical cancer, which represented 10.9% of cases in the current study but now accounts for only 1.4% of female cancer deaths in the United States.[16] Beckman et al[17] document the historic decrease in the incidence of cervical cancer in the United States, from 30 per million in 1930 to 10 per million in 1980; this decrease has been attributed to widespread early screening and treatment procedures that were not available in the past. Other examples of medical advances that have changed the proportion of deaths attributed to primary malignancies, including several found in the current study, may be found. By this reasoning, our cohort of patients who died between 64 and 93 years ago represents essentially untreated human subjects. Compared with more contemporary cohorts, it is therefore more likely that the primary malignancies analyzed in our study have been allowed to run their full pathologic course. Modern chemotherapy and radiation treatment might predictably alter metastatic patterns and reduce metastasis as a whole. Specific examples are discussed in the following discussion.

Breast Cancer

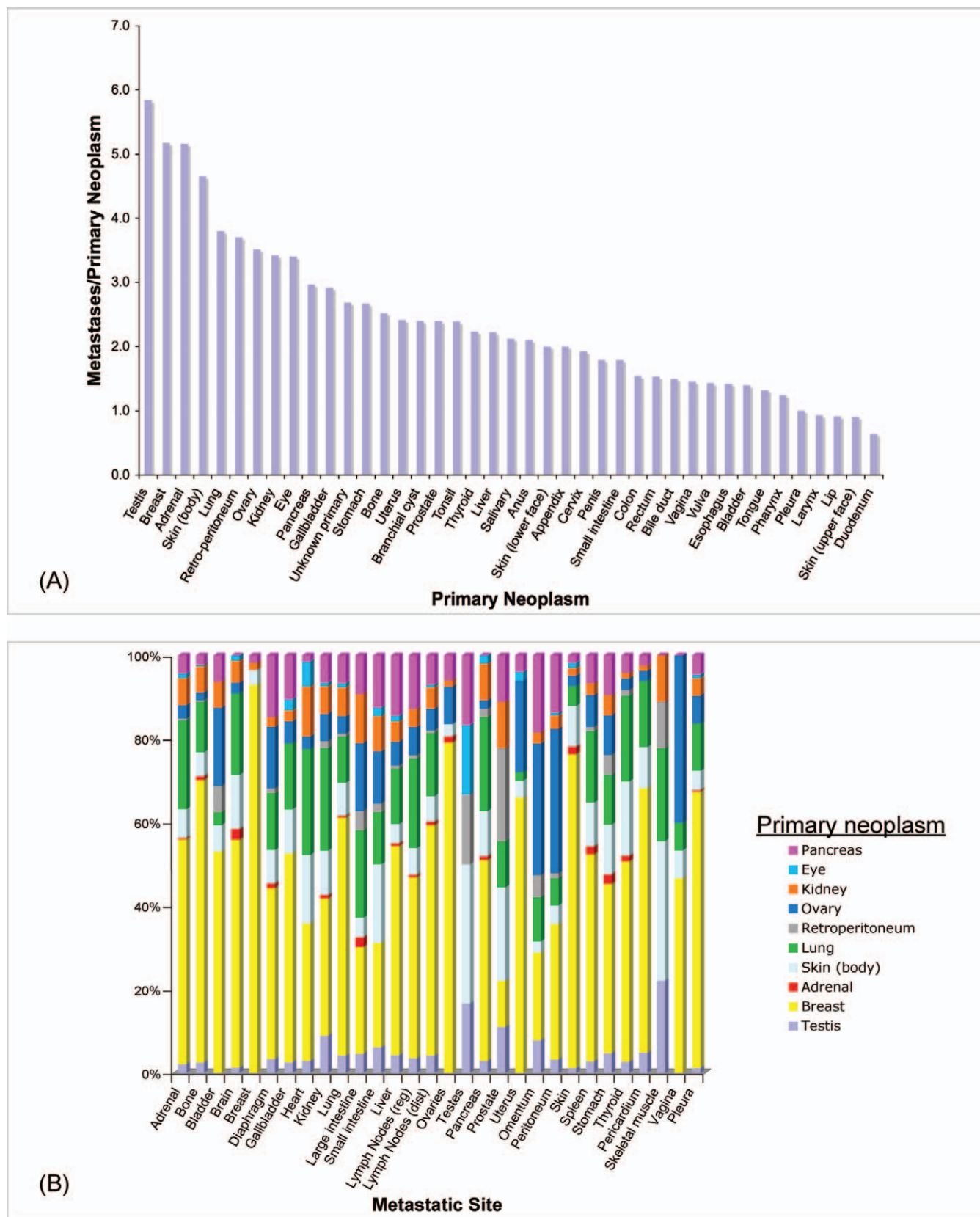Breast cancer accounted for 11.3% of all primary neoplasms, making it the second most common malignancy

Figure 4. *A, Total metastases/total primary cancers by site. B, Relative contribution (as a percentage of the total) to all metastatic sites from each of the 10 primaries that generated the highest average number of primaries per primary cancer in A.*
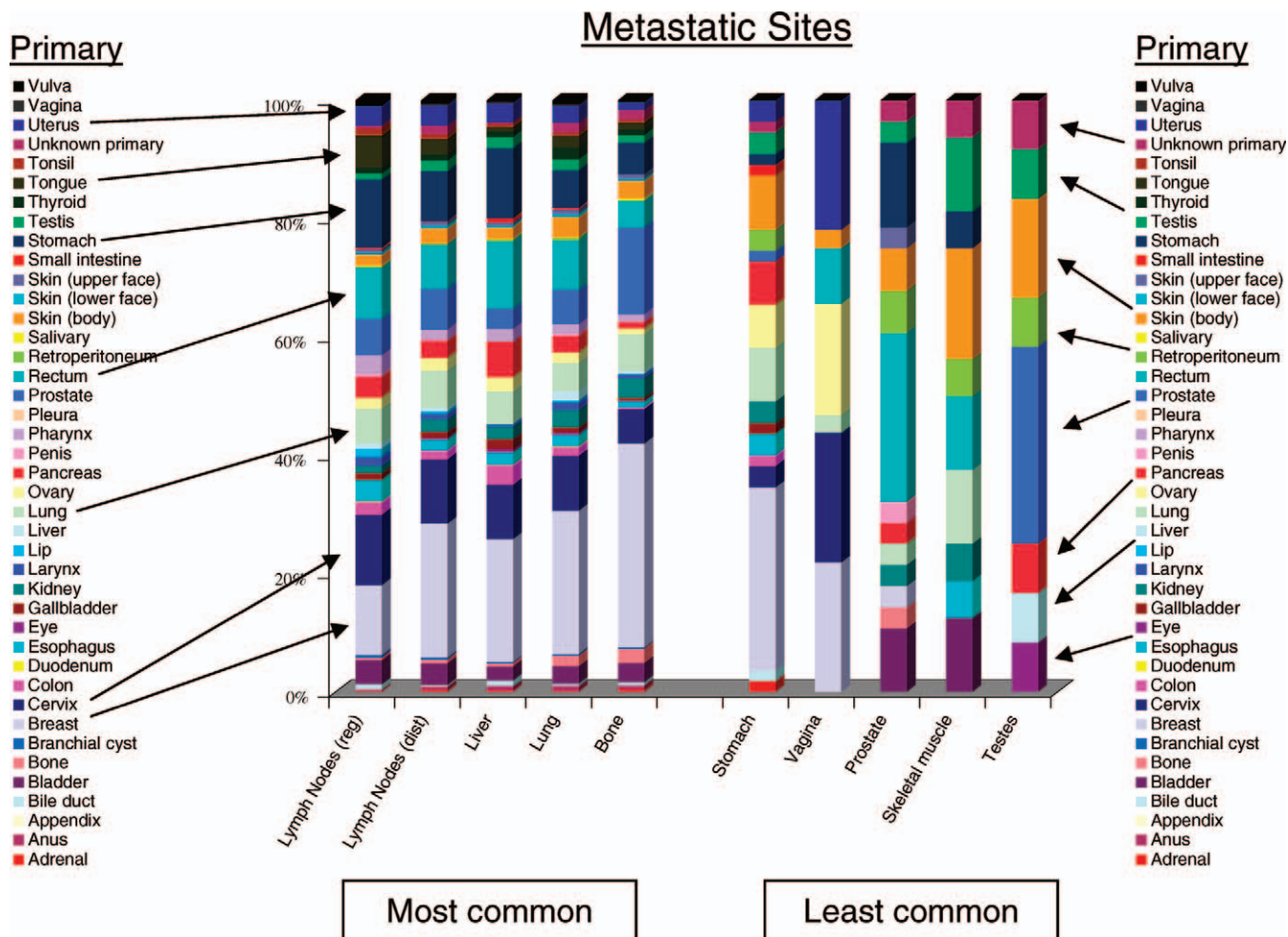
Figure 5. *The percentage of metastases from each primary neoplasm to the 5 most common (left columns) and least common (right columns) metastatic sites. For orientation, arrows are drawn from representative primary neoplasms to their corresponding bar graph locations.*

in this study. Breast cancer is currently the fifth most common cause of cancer death worldwide (502 000 deaths per year), after lung (1.3 million deaths per year), stomach (1 million deaths per year), liver (662 000 deaths per year), and colon (655 000 deaths per year) (http://www.who.int/mediacentre/factsheets/fs297/en/index.html [February 2006]). The robustness with which breast cancer metastasized in the current study is striking: It both represented a high proportion (11.3%) of all primary malignancies (Figure 2) and generated a large number of metastases (5.2 per primary malignancy; Figure 4, A). As a result, breast cancer contributed 23.6% of all metastases (Figure 2), the highest number among all analyzed malignancies. This tendency toward widespread metastasis is consistent with the continuing difficulties in treating primary breast cancer[18,19] and for the frequent identification of breast primaries among cancers that present initially as metastases from an unknown primary site.[20,21]

Breast cancer was nonselective in its metastatic targets (Figure 4, B, yellow bars) and in general contributed the largest proportion of metastases among most different sites, with lymph nodes and lung constituting the most frequent sites (Figure 6). The breast was itself a rare metastatic target in this data set, receiving only 0.7% of all metastases (Figures 1 and 3). Yet 87.1% of all metastases to breast were classified as having originating from the

breast itself in the archival data set (Figure 4, B). This finding is of interest in light of the current difficulties in resolving whether breast lesions more likely represent metastases from contralateral primaries[22] or second (ipsilateral) primary malignancies.[23,24] In retrospect, it therefore appears likely that the former assumption was made at the time that these data were collected and should be evaluated cautiously.

Prostate Cancer

Low-grade prostate cancer is typically an indolent disease that is monitored primarily by serial prostate-specific antigen measurements alone, with interventions dictated largely by abnormal rises in this marker, a practice that may be more beneficial in the patients' quality of life.[25,26] However, metastasis to regional lymph nodes in up to 10.7% of patients without abnormal prostate-specific antigen elevations indicates a need for close clinical monitoring in addition to prostate-specific antigen screening.[27] Frequently cited metastatic targets for prostate cancer, including bone,[9,28,29] lung,[29] and liver,[30] often present with clinical manifestations. The 5 most common metastatic targets for prostate cancer in the current study included regional lymph nodes (26.2%), bone (19.7%), distant lymph nodes (18.4%), lung (12.8%), and liver (7.8%) (Figure 7).
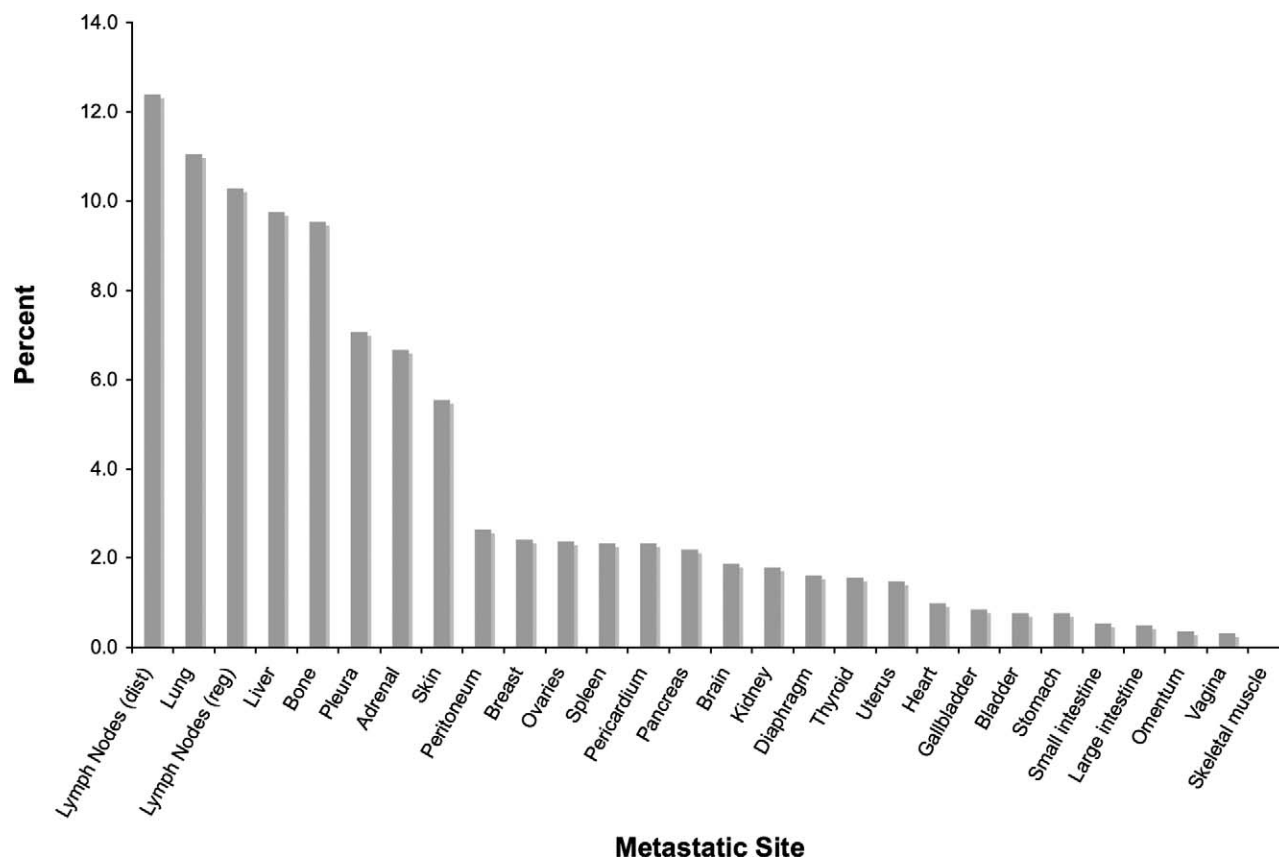
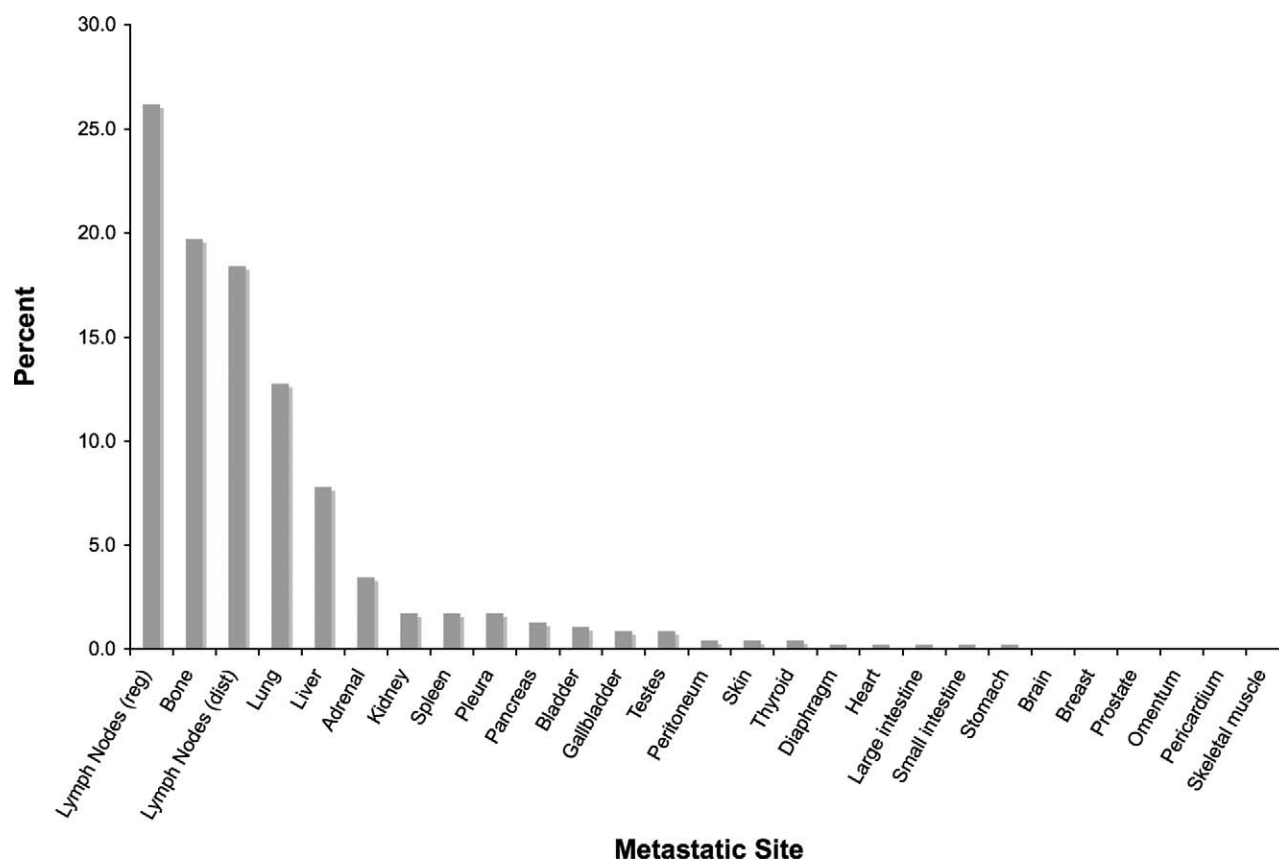**Figure 6.** *Metastases from breast primaries to different metastatic sites.*

Figure 7. *Metastases from prostate primaries to different metastatic sites.*

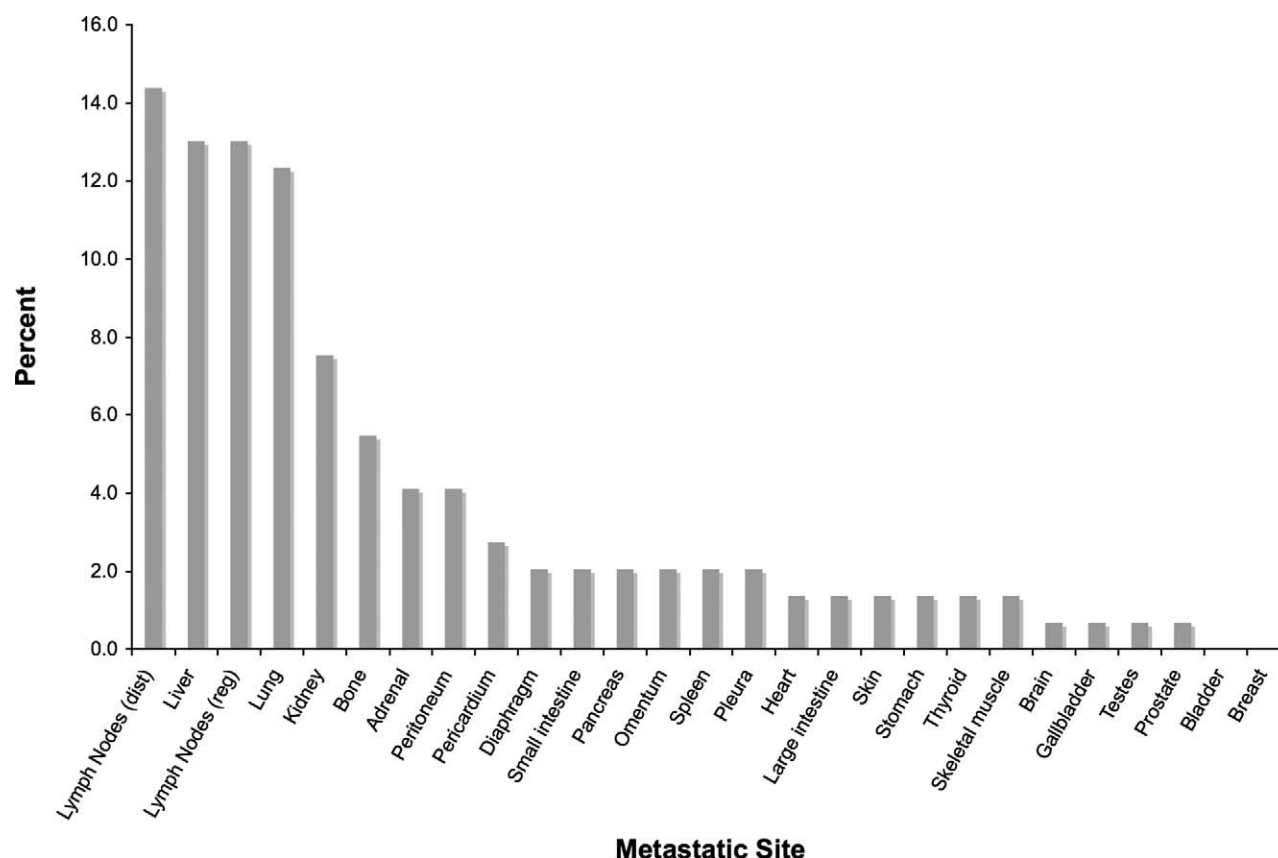*Metastatic Patterns of Cancers*—diSibio & French   **937**

Figure 8. *Metastases from testicular primaries to different metastatic sites.*

Contemporary studies of prostate cancer continue to demonstrate a high degree of metastasis to these sites.[31]

Interestingly, prostate cancers represented a significant proportion (36%) of metastases to the testes (Figure 5), an otherwise unusual metastatic target that harbored only 0.1% of all metastatic lesions in the current study (Figure 3). Contemporary studies also document testes as an important site of subclinical prostatic metastases,[32] albeit one whose significance in disease staging remains controversial.[33] Our results emphasize the importance of monitoring testicular metastases in a patient with known prostate cancer; moreover, metastases to this site by an unknown primary malignancy may eventually prove relatively specific for prostate cancer. This latter hypothesis will require further investigation.

Testicular Cancer

Testicular tumors were rare in this study (0.7% of all primary neoplasms; Figure 2). The 2006 National Center for Health Statistics reported similar rates with an overall incidence of only 1% of all male cancers.[16] Yet testicular cancer remains not only the most common tumor in males between the ages of 15 and 35 years but also the most treatable one, with recently reported survival rates with prompt diagnosis and treatment as high as 90%.[34] Therefore, as testicular cancer frequently presents among young males with cancer from unknown primary site, a thorough documentation of the metastatic behavior of this malignancy that enables prompt diagnosis would be of tremendous value. Once treatment has been initiated, such documentation might also facilitate monitoring of disease progression.

As shown in Figure 2 (compare corresponding blue and red bars), testicular primaries generate a disproportionate number of metastases. Figure 4, A, indicates that each primary malignancy generated an average of 5.8 metastases, the most for any primary malignancy. However, because of the low frequency of this primary malignancy in our study (Figure 2), testicular malignancies generated only 1.5% of all metastases. These metastases were broadly distributed, ranging from 0.9% of pleural to 12.5% of skeletal muscle metastases (Figure 4, B). Figure 8 further quantifies the metastatic behavior of testicular tumors. The most common metastatic sites are distant lymph nodes (14.4%), liver (13%), lung (12.3%), kidney (7.5%), and bone (5.5%). The latter site is notable, in that it represents a rare target for germ cell metastasis for testicular malignancies treated by current protocols. As a result, treatable metastases to bone are occasionally missed in the contemporary setting because of low clinical suspicion.[35]

Of note, Figure 5 shows that testicular cancers metastasized to unusual sites. For example, the prostate gland, a target for only 0.3% of all metastases (Figure 3), nonetheless received a single metastasis. Similarly, although only 0.2% of all metastases were found in skeletal muscle (Figure 3), 2 testicular metastases, or 12.5% of the total, were found there (Figure 5). Given the low absolute number of primary testicular malignancies identified in the current analysis, our findings suggest 2 important clinical implications that might benefit from further, more targeted studies. First, metastasis of an unknown primary to an unusual site (eg, stomach, prostate, skeletal muscle) in a male patient between the ages of 15 and 35 years might

raise suspicion for a testicular origin. Second, these uncommon sites might be of value in monitoring relapse among treated patients with known testicular cancers.

CONCLUSION

The present study was based on an unusually rich set of autopsy data, comprising a large number of patients and a broad array of cancer types and metastases. Furthermore, as a uniquely broad study of actual postmortem tissues on patients who died before the advent of contemporary therapies, the findings of this study likely represent a close approximation for the progression of untreated malignancies in humans. Attesting to the unique value of these data, to our knowledge there are no studies analogous to the current one in either breadth or scale in the current literature. Given the current trend toward fewer hospital autopsies,[2,3,36] it is difficult to envision future studies on postmortem tissue of this scale. Fortunately, several interesting implications emerge from the current study that, in conjunction with more contemporary, targeted studies, may prove a useful baseline in patient management. Moreover, it is our hope that this baseline will facilitate further studies to clarify the clinical and molecular behaviors of specific malignancies cited in this study, particularly those that occurred with less frequency.

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