CANCER IN THE SPINE
CURRENT CLINICAL ONCOLOGY

Maurie Markman, MD, SERIES EDITOR

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Recent advances in medical treatment have dramatically changed our approach to many forms of cancer. Nowhere is this more apparent than in our approach to patients with cancer of the spinal column. A scant 30 years ago, spinal tumors were considered largely untreatable. Tumor resection was considered futile, if not mutilating, and radiotherapy was limited in dose and approach to what the spinal cord could bear. Diagnosis often came late, when treatment could only be brought to bear on the sequelae of tumor growth—spinal cord compression and mechanical instability and pain. The seemingly inevitable progression from spinal metastasis to fracture, intractable pain, cord compression, and paresis left the patient bedridden, malnourished, and narcotized, and easy prey for the bedsores, pneumonia, or urinary tract infections that would eventually take their lives. Even today many physicians quietly consider the appearance of a spinal metastasis to be the death knell for their patients with carcinoma.

Early diagnosis, improved screening, and better follow-up screening of those with known primary disease have improved our ability to recognize spinal tumors at an early and more manageable stage. Advances in imaging technology and histological techniques have improved diagnostic accuracy and reduced the need for more invasive techniques that carry greater cost, morbidity, and discomfort for the patient.

Although advances in chemotherapeutic and medical management regimens have improved long-term survival and cure rates for patients with many forms of cancer, advances in supportive medical care have reduced the impact of many attendant systemic problems that rendered patients “too sick” for aggressive therapy or surgery. Improved perioperative and intra-operative management now allows us to accomplish radical resection of spinal tumors considered inoperable just a decade ago.

Advances in radiotherapeutic modalities have simultaneously improved the efficacy of tumor treatment while reducing the collateral damage inherent in approaches of the past. The ability to focus therapy on the tumor itself reduces the risk of injury to the spinal cord and to the overlying skin, permitting more aggressive therapy with a lower complication rate. Newer therapeutic modalities such as brachytherapy and intra-operative radiotherapy allow us to precisely boost radiation doses to tumor foci without causing damage to the sensitive structures nearby.

Improvements in surgical technique have resulted in better survival and cure rates for patients with both primary and metastatic lesions. Prolonged bed rest, necessitated by surgical resection and spinal cord decompression, is largely a thing of the past. Advances in surgical technique, and a quantum leap in spinal instrumentation, now allow surgeons to radically resect lesions at any level of the spinal column with the full expectation that the patient will be up and out of bed within days of surgery. Rapid return to function and independence, combined with more reliable pain relief, makes surgical care a reasonable consideration for many patients previously thought beyond help. New, minimally invasive surgical techniques can provide dramatic pain relief, with greatly reduced morbidity, in even the sickest patients.

Advances in end-of-life care cannot be overlooked either. Patients with cancer fear pain and loss of independence. Improvements in medical pain management allow patients to function independently despite advanced disease, with less impairment of mental function.

More than ever before, care of the patient with cancer of the spinal column requires interdisciplinary cooperation and coordination. Injudicious use of one modality, even in terms of timing, can make it difficult or impossible to safely apply other treatment options in a given patient. A multidisciplinary team, with a broad perspective as to the relative value and risk associated with the many treatment options now available, has the best chance for coordinating care of these challenging patients so that treatment effect is maximized and complications and injury are avoided. Fortunately, the growing recognition that there is much to be gained—that these patients will benefit from an aggressive, coordinated approach to cancer management—has spurred greater interest in their care and the collaboration needed to provide that care.

The goal of Cancer in the Spine: Comprehensive Care is to provide an overview of the many disciplines involved in caring for patients with cancer of the spine, and to provide some guidance as to how these different modalities may be combined to provide the most effective treatment for today’s patients. Although the chapters that follow are rich in technical descriptions and survival data, care and compassion remain the fundamental properties that any physician must bring to these cases. No patient is “too sick” to be helped. There is no such thing as “benign neglect.” Sometimes, in the end, all we can offer is to be there, and sometimes, that is what our patients need the most.

Robert F. McLain, MD
# Contents

*Preface............................................................................................................................................................................ v*
*Contributors ..................................................................................................................................................................... ix*

1 Cancer of the Spine: How Big Is the Problem? ................................................................. 1
   Kai-Uwe Lewandrowski, Gordon R. Bell, and Robert F. McLain

2 Metastatic Disease to the Musculoskeletal System ...................................................... 7
   David G. Hicks

3 The Pathophysiology of Spinal Metastases ................................................................. 17
   Daisuke Togawa and Kai-Uwe Lewandrowski

4 Tumor Behavior: Barriers to Growth and Spread ..................................................... 25
   Robert F. McLain

5 Fundamentals of Cancer Treatment: Effects of Chemotherapy on Neoplastic Cells .............................................. 31
   Sujith Kalmadi and Derek Raghavan

6 The Role of Surgical Therapy: Principles of Effective Surgical Treatment .............. 43
   Robert F. McLain

7 Presenting History and Common Symptoms of Spine Tumors .................................... 49
   Daniel Shedid and Edward C. Benzel

8 Physical Examination: Signs of Pathology and the Spine Examination .................... 55
   Eric Truumees

9 Imaging: Screening for Spinal Disease ........................................................................ 67
   A. Jay Khanna, Mesfin A. Lemma, Bruce A. Wasserman, and Robert F. McLain

10 Imaging of the Spine ......................................................................................................... 73
    A. Jay Khanna, Michael K. Shindle, and Bruce A. Wasserman

11 Laboratory Studies and Diagnostic Work-Up of Bony Lesions in the Spine ............ 83
    Kai-Uwe Lewandrowski, Robert F. McLain, and Henry J. Mankin

12 Principles of Medical Management ............................................................................. 93
    Tarek Mekhail, Rony Abou-Jawde, and Maurie Markman

13 Multiple Myeloma and Plasmacytoma ......................................................................... 101
    Mohamad Hussein

14 Lymphoma ...................................................................................................................... 107
    Ronald M. Sobecks

15 Metastatic Breast Carcinoma ....................................................................................... 117
    John Hill and G. Thomas Budd

16 Genitourinary Oncology: Prostate, Renal, and Bladder Cancer ............................... 123
    Robert Dreicer

17 Spinal Metastases From Gastrointestinal Malignancies ............................................ 131
    Mellar P. Davis

18 Lung Cancer .................................................................................................................... 141
    Jigar Shah and Tarek Mekhail

19 Medical Management of Thyroid Cancer .................................................................. 157
    Ajay Sood and S. Sethu Reddy

20 Carcinoma of the Unknown Primary ................................................................ .......... 165
    Thomas E. Hutson and Ronald M. Bukowski
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Authors</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Primary Tumors of the Spine</td>
<td>Rex C. Haydon and Frank M. Phillips</td>
<td>171</td>
</tr>
<tr>
<td>22</td>
<td>Common Radiotherapy Techniques for Spinal Tumors</td>
<td>Mohamed A. Elshaikh and Roger M. Macklis</td>
<td>189</td>
</tr>
<tr>
<td>23</td>
<td>Spinal Radiotherapy for the Pediatric Patient: Indications, Special Technical Considerations, and Long-Term Consequences</td>
<td>Adir Ludin</td>
<td>197</td>
</tr>
<tr>
<td>24</td>
<td>Conformal Radiotherapy for Spinal Lesions</td>
<td>Richard L. Crownover</td>
<td>205</td>
</tr>
<tr>
<td>25</td>
<td>Photon- and Proton-Beam Radiotherapy in the Treatment of Spine Tumors</td>
<td>Thomas F. DeLaney, Michael J. Harris, Francis J. Hornicek, and Robert F. McLain</td>
<td>211</td>
</tr>
<tr>
<td>26</td>
<td>Spinal Metastasis: Indications for Surgery</td>
<td>Iain H. Kalfas</td>
<td>219</td>
</tr>
<tr>
<td>27</td>
<td>Biopsy: Principles and Approaches</td>
<td>Paul Park, Frank LaMarca, and Robert F. McLain</td>
<td>227</td>
</tr>
<tr>
<td>28</td>
<td>Problem-Based Decision Making</td>
<td>Michael P. Steinmetz, Anis O. Mekhail, and Edward C. Benzel</td>
<td>233</td>
</tr>
<tr>
<td>29</td>
<td>Spinal Cord and Nerve Root Decompression</td>
<td>Keith R. Lodhia, Paul Park, and Gregory P. Graziano</td>
<td>239</td>
</tr>
<tr>
<td>30</td>
<td>Metastatic Disease of the Cervical Spine</td>
<td>Ashley R. Poynton, Mark H. Bilsky, Federico P. Girardi, Patrick J. Boland, and Frank P. Cammisa, Jr.</td>
<td>247</td>
</tr>
<tr>
<td>31</td>
<td>Metastatic Disease of the Thoracolumbar Spine</td>
<td>L. Brett Babat and Robert F. McLain</td>
<td>255</td>
</tr>
<tr>
<td>32</td>
<td>Complex Lumbosacral Resection and Reconstruction Procedure</td>
<td>Daryl R. Fourney and Ziya L. Gokaslan</td>
<td>265</td>
</tr>
<tr>
<td>33</td>
<td>Neoplastic Disease of the Spinal Cord and the Spinal Canal</td>
<td>Daniel Shedid and Edward C. Benzel</td>
<td>279</td>
</tr>
<tr>
<td>35</td>
<td>Single-Stage Posterolateral Transpedicle Approach With Circumferential Decompression and Instrumentation for Spinal Metastases</td>
<td>Mark H. Bilsky, Todd Vitaz, and Patrick Boland</td>
<td>295</td>
</tr>
<tr>
<td>36</td>
<td>Primary Benign Spinal Tumors</td>
<td>Gordon R. Bell</td>
<td>303</td>
</tr>
<tr>
<td>37</td>
<td>Surgical Treatment of Primary Malignant Tumors</td>
<td>Branco Prpa and Robert F. McLain</td>
<td>311</td>
</tr>
<tr>
<td>38</td>
<td>Complications of Surgical and Medical Care: Anticipation and Management</td>
<td>Rex A. W. Marco and Howard S. An</td>
<td>323</td>
</tr>
<tr>
<td>39</td>
<td>Bracing for Patients With Spinal Tumors</td>
<td>Kai-Uwe Lewandrowski, Robert F. McLain, and Edward C. Benzel</td>
<td>337</td>
</tr>
<tr>
<td>40</td>
<td>Rehabilitation in Patients With Tumors of the Spinal Column</td>
<td>Leah Moinzadeh and Sandee Patti</td>
<td>343</td>
</tr>
<tr>
<td>41</td>
<td>The Management of Pain in Spinal Malignancies</td>
<td>Susan B. LeGrand and Declan Walsh</td>
<td>349</td>
</tr>
<tr>
<td>42</td>
<td>Surveillance and Screening During Disease-Free Survival</td>
<td>Richard Placide, Kai-Uwe Lewandrowski, and Robert F. McLain</td>
<td>361</td>
</tr>
<tr>
<td>43</td>
<td>When is Enough, Enough?</td>
<td>Edward C. Benzel, Michael P. Steinmetz, Ann M. Henwood, L. Brett Babat, and Anis O. Mekhail</td>
<td>365</td>
</tr>
</tbody>
</table>

Index ................................................................. 371
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1 Cancer of the Spine

How Big Is the Problem?

KAI-UWE LEWANDROWSKI, MD, GORDON R. BELL, MD, AND ROBERT F. MCLAIN, MD

CONTENTS

US CANCER STATISTICS
FREQUENCY OF SPINAL TUMORS
METASTATIC SPINE TUMORS: AGE AND GENDER
LOCATION OF SPINAL METASTASES
MAGNITUDE OF THE PROBLEM
THE CHALLENGE
REFERENCES

1. US CANCER STATISTICS

For the second consecutive year, the Centers for Disease Control and Prevention (CDC) and the National Cancer Institute have released an annual US Cancer Statistics report (1). Published in collaboration with the North American Association of Central Cancer Registries, this report provides detailed information on cancer incidence, surveillance, epidemiology, and end results for 66 selected primary cancer sites and subsites for males (Table 1), 70 selected primary cancer sites and subsites for females (Table 2), and for all cancer sites combined (Figs. 1 and 2). In addition, these data have been analyzed with regard to geographic area, race, sex, and age (Table 3). According to the CDC and National Cancer Institute, 84% of the US population is covered in the 2000 surveillance report (1).

2. FREQUENCY OF SPINAL TUMORS

As indicated by the 2000 CDC US Cancer Statistics (1), the most common primary malignancies for men include prostate, lung, and colon with the incidence ranging from 160.4 to 65.0 cases per 100,000. For women, the leading primary malignancy is breast cancer followed by lung and colon cancer with the incidence ranging from 128.9 to 47.0 cases per 100,000. By comparison, spinal tumors are very rare. A review of data obtained from the Leeds Tumor Registry revealed that only 2.8% of the 1950 cases had tumors in the spine, which can arise from bone, cartilage, and rarely from other tissues (as is the case with lipomas, meningiomas, and neurofibromas) (2). Primary bone tumors in the spine are extremely rare as well. Of the 2000 sarcomas arising in bone each year in the United States, only 10% are found in the spine (3). In fact, the incidence of primary tumors of the spine per 100,000 persons per year is estimated as between 2.5 and 8.5 (3).

In comparison, the vast majority (95%) of the clinically relevant spinal tumors are metastases (4). More than 60% of these metastases arise from myelomas, lymphomas, or adenocarcinomas of the breast, lung, and prostate (Table 3) (5). Metastases in the axial and appendicular skeleton are extremely common and may be present in up to 70% of the patients with advanced adenocarcinoma before death (4). With respect to breast cancer, this rate may be as high as 85% (5). These clinical observations are corroborated by autopsy studies, which showed that metastases are present in nearly 80% of advanced-stage cancer patients (6).

3. METASTATIC SPINE TUMORS: AGE AND GENDER

Visceral or bony metastases should be expected in the majority of patients with advanced-stage disease at some point during the course of their illness (7). This becomes particularly apparent in patients older than 40 yr. As shown in Table 3, the incidence of carcinomas, myelomas, and lymphoma is sharply increased (8). In general, spinal metastases are considered a preterminal event, which indicates that a cancer may no longer be curable. In other words, regional disease has become a systemic illness. Of the 18,000 patients in the United States diagnosed annually with vertebral metastases, men are disproportionately more affected, with a male to female ratio of 3:2 (9).

4. LOCATION OF SPINAL METASTASES

The spinal column is the most common site of skeletal or osseous metastases (10). Rates of metastatic spread to the spine
Table 1
Invasive Cancer Incidence Rates for the 15 Primary Sites With the Highest Age-Adjusted Incidence Rates Within Race-Specific Categories

<table>
<thead>
<tr>
<th>All races</th>
<th>White</th>
<th>Black</th>
<th>Asian/Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate</td>
<td>160.4</td>
<td>150.5</td>
<td>233.8</td>
</tr>
<tr>
<td>2. Lung and bronchus</td>
<td>87.9</td>
<td>86.8</td>
<td>107.1</td>
</tr>
<tr>
<td>3. Colon and rectum</td>
<td>65.0</td>
<td>64.5</td>
<td>67.3</td>
</tr>
<tr>
<td>4. Urinary bladder</td>
<td>37.8</td>
<td>39.9</td>
<td>18.2</td>
</tr>
<tr>
<td>5. Non-Hodgkin’s lymphoma</td>
<td>21.6</td>
<td>22.0</td>
<td>17.4</td>
</tr>
<tr>
<td>6. Melanomas of the skin</td>
<td>19.4</td>
<td>21.0</td>
<td>17.1</td>
</tr>
<tr>
<td>7. Kidney and renal pelvis</td>
<td>16.4</td>
<td>16.4</td>
<td>16.8</td>
</tr>
<tr>
<td>8. Oral cavity and pharynx</td>
<td>15.7</td>
<td>15.3</td>
<td>15.4</td>
</tr>
<tr>
<td>9. Leukemias</td>
<td>14.5</td>
<td>14.9</td>
<td>15.1</td>
</tr>
<tr>
<td>10. Pancreas</td>
<td>12.1</td>
<td>11.8</td>
<td>12.1</td>
</tr>
<tr>
<td>11. Stomach</td>
<td>10.5</td>
<td>9.5</td>
<td>12.0</td>
</tr>
<tr>
<td>12. Esophagus</td>
<td>8.5</td>
<td>8.2</td>
<td>10.9</td>
</tr>
<tr>
<td>13. Larynx</td>
<td>7.8</td>
<td>8.2</td>
<td>10.5</td>
</tr>
<tr>
<td>14. Brain and ONS</td>
<td>7.7</td>
<td>7.4</td>
<td>9.5</td>
</tr>
<tr>
<td>15. Liver and IBD</td>
<td>7.4</td>
<td>6.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Source: Center for Disease Control US Cancer Statistics, 2000 Incidence Report: Top 15 Cancer Sites. US males by race, rates per 100,000. ONS, other nervous system; IBD, interlobular bile ducts.

Table 2
Invasive Cancer Incidence Rates for the 15 Primary Sites With the Highest Age-Adjusted Incidence Rates Within Race-Specific Categories

<table>
<thead>
<tr>
<th>All races</th>
<th>White</th>
<th>Black</th>
<th>Asian/Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast</td>
<td>128.9</td>
<td>131.4</td>
<td>108.3</td>
</tr>
<tr>
<td>2. Lung and bronchus</td>
<td>52.5</td>
<td>53.8</td>
<td>51.9</td>
</tr>
<tr>
<td>3. Colon and rectum</td>
<td>47.0</td>
<td>46.2</td>
<td>46.5</td>
</tr>
<tr>
<td>4. Corpus and uterus, NOS</td>
<td>23.5</td>
<td>24.2</td>
<td>18.4</td>
</tr>
<tr>
<td>5. Ovary</td>
<td>15.8</td>
<td>16.4</td>
<td>12.9</td>
</tr>
<tr>
<td>6. Non-Hodgkin’s lymphoma</td>
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<td>15.8</td>
<td>12.6</td>
</tr>
<tr>
<td>7. Melanomas of the skin</td>
<td>12.4</td>
<td>13.8</td>
<td>10.5</td>
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<tr>
<td>8. Thyroid</td>
<td>10.7</td>
<td>11.0</td>
<td>10.3</td>
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<tr>
<td>9. Urinary bladder</td>
<td>9.8</td>
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<td>8.8</td>
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<tr>
<td>10. Pancreas</td>
<td>9.5</td>
<td>9.1</td>
<td>8.6</td>
</tr>
<tr>
<td>11. Cervix uteri</td>
<td>9.2</td>
<td>8.9</td>
<td>8.6</td>
</tr>
<tr>
<td>12. Leukemias</td>
<td>8.7</td>
<td>8.6</td>
<td>7.0</td>
</tr>
<tr>
<td>13. Kidney and renal pelvis</td>
<td>8.4</td>
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<td>8.5</td>
</tr>
<tr>
<td>14. Oral cavity and pharynx</td>
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<td>6.0</td>
<td>6.5</td>
</tr>
<tr>
<td>15. Brain and ONS</td>
<td>5.5</td>
<td>5.8</td>
<td>5.1</td>
</tr>
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Source: Center for Disease Control United States Cancer Statistics, 2000 Incidence Report: Top 15 Cancer Sites. US Females by race, rates per 100,000. ONS, other nervous system.

Vary widely according to the primary tumor of origin (Table 5). However, autopsy studies indicated that vertebral metastases increase in frequency in a caudal direction along the vertebral column (11–14). This distribution appears to correlate with the increasing volume of bone marrow within the vertebral bodies from the cervical to the lumbar regions of the spine. For example, breast cancer metastases account for nearly 54% of all spine metastases among women (15). The most frequent locations of tumors, in descending order, are the vertebrae (85%), the paravertebral spaces (10–15%), the epidural space (<5%), and intradural/intramedullary (16). As demonstrated in a large series of 1585 patients with symptomatic epidural deposits, the vast majority (70.3%) of lesions are located in the thoracic and thoracolumbar spine, 21.6% in the lumbosacral spine, and 8.1% in the cervical spine (17). More recently, it has been suggested that as many as 20% of spinal metastases arise in the cervical segments (16–18). Because 10 to 38% of patients have metastases in multiple noncontiguous spine sites (7,18), skip lesions in other areas of the spine should be suspected particularly in patients with advanced-stage disease.

5. MAGNITUDE OF THE PROBLEM

Of the one million new cases of cancer diagnosed annually, metastases will develop in two-thirds of the patients (11,20).
Considering that 80% of these patients will be diagnosed with spinal metastases during the course of their disease, it is estimated that approximately 500,000 patients will present with spinal metastases each year. Thirty-six percent of spinal metastases are asymptomatic and discovered incidentally (16). Symptomatic spinal cord involvement has been estimated to occur in 18,000 patients per year (21). With continued advances in the treatment of primary disease and local recurrences, patients are living longer and more frequently require treatment for symptomatic distant metastases. Bearing in mind that detection methods continue to improve, that patients survive longer, and that our population is aging, it is anticipated that the prevalence...
Table 4
Prevalence and Prognosis of Metastatic Cancer

<table>
<thead>
<tr>
<th>Primary tumor</th>
<th>Percent of total spine metastases (2748 cases)</th>
<th>Prevalence to bone in advanced disease (%)</th>
<th>Prevalence to spine in advanced disease (%)</th>
<th>Median survival (mo)</th>
<th>5-yr survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breasts</td>
<td>21</td>
<td>65–75</td>
<td>16.5–37</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Prostate</td>
<td>7.5</td>
<td>65–90</td>
<td>9.2–15</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>Lung</td>
<td>14</td>
<td>30–45</td>
<td>12–15</td>
<td>&lt;6</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Kidney</td>
<td>5.5</td>
<td>20–30</td>
<td>3–6.5</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal (carcinoid)</td>
<td>5</td>
<td>–</td>
<td>4.7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thyroid</td>
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<td>60</td>
<td>4</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Melanoma</td>
<td>–</td>
<td>14–55</td>
<td>1–2</td>
<td>&lt;6</td>
<td>&lt;5</td>
</tr>
</tbody>
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Table 5
Distribution of Metastases in the Spine

<table>
<thead>
<tr>
<th></th>
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<td>Cervical and cervical thoracic</td>
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<td>17</td>
<td>3</td>
<td>14</td>
<td>8</td>
<td>12</td>
<td>9</td>
<td>13</td>
<td>127</td>
<td>8.1</td>
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<td>Thoracic and thoracic lumbar</td>
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<td>186</td>
<td>87</td>
<td>50</td>
<td>108</td>
<td>90</td>
<td>83</td>
<td>75</td>
<td>116</td>
<td>74</td>
<td>163</td>
<td>1115</td>
<td>70.3</td>
</tr>
<tr>
<td>Lumbar and sacral</td>
<td>30</td>
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<td>5</td>
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<td>12</td>
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<td>21</td>
<td>69</td>
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<td>60</td>
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<td>105</td>
<td>139</td>
<td>104</td>
<td>197</td>
<td>109</td>
<td>218</td>
<td>1585</td>
<td></td>
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</tbody>
</table>

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of symptomatic spinal metastases is likely to increase substantially in the future, posing an ever growing challenge to the spine surgeon (22).

6. THE CHALLENGE

The growing number of patients with metastatic processes in the spine requires application of sound oncological principles to reduce the morbidity and mortality associated with biopsies and surgical interventions. Continued advances in spinal instrumentation and perioperative supportive care are expected to permit more aggressive and effective surgical treatments, including the en-bloc removal of tumors. This will require a close working relationship between the patient, the oncologist, and the surgeon. A multidisciplinary oncology service is key to providing more effective palliation for advanced-stage cancer patients. Moreover, patient education is essential to allow the patient to make better informed, appropriate choices regarding his or her management.

REFERENCES

1. INTRODUCTION

Bone is a dynamic tissue that undergoes continuous remodeling. It goes through a balanced process that entails repeated cycles of bone resorption coupled with synthesis of new bone matrix (Fig. 1). These remodeling cycles are influenced by an individual’s age, endocrine and nutritional status, and level of physical activity. This ongoing tissue turnover is important for meeting the often conflicting need of the skeleton to maintain structural support for the body while also providing a source of ions for mineral homeostasis. The maintenance of skeletal mass in the face of continuous bone remodeling requires the coordinated activities of osteoblasts and osteoclasts, the two cell types responsible for skeletal matrix formation and resorption (1) (Fig. 1). Advances in our understanding of the precise mechanisms that control the cellular interactions and coupled activities of these two cell types have provided new insight into a number of diseases affecting the skeleton. These disorders are characterized by an imbalance of remodeling with subsequent increase in bone resorption, decreased bone mass, and loss of skeletal stability and integrity. This is particularly true for neoplastic diseases, in which a number of common human malignancies have a propensity to spread to the skeleton, resulting in significant morbidity and mortality from bone destruction (2).

1.1. METASTATIC DISEASE TO THE SKELETON

Tumor metastasis is the leading cause of death for patients with cancer, and the skeletal system is one of the most common sites to be affected by metastatic disease. However, not all tumors share the same likelihood of dissemination to the skeleton. Of the cancers that spread to bone, carcinomas of the breast and the prostate possess a special affinity, accounting for more than 80% of all cases of metastatic skeletal disease (2). Other tumors that frequently spread to the skeleton include carcinomas of the lung, kidney, and thyroid (2). This special osteotrophism or affinity to metastasize to bone involves characteristics of these tumors that allow them to establish and grow in bone, as well as unique features of the bone microenvironment, which makes the skeleton a particularly congenial place for these cells (6). More than 100 yr ago, Stephen Paget referred to this as the “seed and soil” hypothesis, to explain the special affinity of breast cancer for the “fertile soil” of the bone microenvironment (7).

1.2. CARCINOMA OF THE BREAST

Breast cancer is one of the most common malignancies in women. Up to one-third of women with early stage breast cancer will eventually succumb to their disease and many of them will have developed bone metastases during the course of their...
Bone is a dynamic, metabolically active tissue. In order to maintain structural support for the body while providing a source of ions for mineral homeostasis, the skeleton must undergo continuous remodeling. This is a balanced process that entails repeated cycles of bone resorption by osteoclasts coupled with synthesis of new bone matrix by osteoblasts. An individual’s age, endocrine and nutritional status, and level of physical activity influence these remodeling cycles. The maintenance of bone mass in the face of continuous bone turnover of approx 10% of the adult skeleton and cortical and trabecular bone is ongoing, and results in an annual turnover of approx 1% of the adult skeleton (14). These bone remodeling cycles are both temporally and spatially “coupled” and involve regulatory mechanisms that closely link the activities of these two cell types (Fig. 2). Bone resorption is, for the most part, a unique function of the osteoclast (15), a specialized multinucleated polykaryon, which is derived from the hematopoietic monocyte/macrophage lineage (16). The initial steps in this temporal sequence involve the proliferation of immature osteoclast precursors, differentiation into osteoclasts, matrix adherence, formation of a specialized ruffled border between the cell and the bone surface, and subsequent resorption (1). The recognition and attachment of the osteoclast to bone matrix is controlled by specific integrin binding (αvβ3) (17). Integrin binding to the bone matrix signals the osteoclast to organize the cytoskeleton leading to polarization of the cytoplasm and the development of a specialized ruffled border that permits the establishment of an isolated space adjacent to the underlying bone surface (18). The osteoclast then resorbs bone by the production of proteolytic enzymes and hydrogen ions, which are exported into the localized environment under the ruffled border of the cell (19). A proton pump, similar to the vacuolar ATPase in the intercalated cells of the kidney, pumps hydrogen ions across the membrane of the cell, and lysosomal enzymes are also released creating the optimal conditions for the degradation of the matrix (19). The conclusion of bone resorption is

2. THE BIOLOGY OF BONE REMODELING

Bone is a dynamic, metabolically active tissue throughout life. After skeletal growth is complete, remodeling of both cortical and trabecular bone is ongoing, and results in an annual turnover of approx 10% of the adult skeleton (14). These bone remodeling cycles are both temporally and spatially “coupled” and involve regulatory mechanisms that closely link the activities of these two cell types (Fig. 2). Bone resorption is, for the most part, a unique function of the osteoclast (15), a specialized multinucleated polykaryon, which is derived from the hematopoietic monocyte/macrophage lineage (16). The initial steps in this temporal sequence involve the proliferation of immature osteoclast precursors, differentiation into osteoclasts, matrix adherence, formation of a specialized ruffled border between the cell and the bone surface, and subsequent resorption (1). The recognition and attachment of the osteoclast to bone matrix is controlled by specific integrin binding (αvβ3) (17). Integrin binding to the bone matrix signals the osteoclast to organize the cytoskeleton leading to polarization of the cytoplasm and the development of a specialized ruffled border that permits the establishment of an isolated space adjacent to the underlying bone surface (18). The osteoclast then resorbs bone by the production of proteolytic enzymes and hydrogen ions, which are exported into the localized environment under the ruffled border of the cell (19). A proton pump, similar to the vacuolar ATPase in the intercalated cells of the kidney, pumps hydrogen ions across the membrane of the cell, and lysosomal enzymes are also released creating the optimal conditions for the degradation of the matrix (19). The conclusion of bone resorption is

illness (8). A significant percentage (50–70%) of patients with metastatic breast cancer will have skeletal involvement, contributing significantly to their morbidity (9). In approx 50% of these patients, bone will be the predominant site of metastatic spread and in 20–25% of these patients the skeleton will be the only site of metastasis (9). Approximately 80% of patients with bone-limited disease at the time of diagnosis developed skeletal complications (bone pain, fracture, and hypercalcemia), as will 60% of those with bone and visceral disease and 21% of those with no bone disease (10).

1.3. CARCINOMA OF THE PROSTATE

Likewise, metastatic disease with bone loss and skeletal complications is common in patients with carcinoma of the prostate. Although relatively few patients will manifest bone metastases at initial diagnosis, a significant portion of these men will develop skeletal complications over the course of their disease (11). One-third of patients will experience some adverse skeletal manifestation, including vertebral collapse requiring spinal orthosis, spinal cord compression, and pathological bone fracture (12). Patients with high-grade tumors and those with progressive disease have the highest risk for bone metastases (11). The tumor will have spread to the skeleton in 85–100% of patients who die of their disease (13).

To help explain the interactions between tumor cells that metastasize to bone and the skeletal microenvironment, this chapter first reviews the biology of normal bone remodeling and some of the biological principles of metastasis. Some intriguing animal model studies that have added immensely to the understanding of this complex process are described. Finally, some of the current strategies used to treat this devastating complication of malignancy are briefly discussed.
most likely mediated by osteoclast apoptosis, however, the signals are still poorly understood. Drugs that inhibit bone resorption, such as bisphosphonates, induce osteoclast apoptosis, therefore, the cessation of osteoclast activity may be as important as their formation in the regulation of bone remodeling (20).

A large number of hormones, growth factors, inflammatory mediators, and cytokines are all known to stimulate osteolytic bone resorption through stimulation of osteoclast formation and function (21). How such a diverse group of factors (e.g., parathyroid hormone [PTH], parathyroid hormone-related protein promoter [PTHrP], vitamin D3, interleukin [IL]-1, IL-6, tumor necrosis factor [TNF], and prostaglandins) interact with receptors on osteoblast/stromal cells stimulating the expression of M-CSF and RANKL is not well understood (20). M-CSF is a secreted protein, which interacts with its receptor on monocyte/macrophage progenitors causing these cells to become committed to the osteoclast lineage, creating a pool of osteoclastic precursors. RANKL is expressed on the cell membranes of osteoblasts/stromal cells. (C) When osteoclast precursors, which express the receptor RANK, are exposed to RANKL through cell-to-cell interaction with osteoblasts/stromal cells, they will differentiate into mature activated osteoclasts. RANKL can also bind with OPG, which is a soluble receptor for RANKL, and acts as a decoy in the RANK–RANKL signaling system to inhibit osteoclastogenesis. M-CSF, RANKL, and OPG appear to be the molecular mediators of osteoclastogenesis, and provide a common pathway mediating the activation of bone resorption and controlling physiological bone turnover. The ratio of RANKL:OPG is an important determinant of osteoclast formation and activity and directly determines the rate of both physiological and pathological osteoclastic bone resorption.

Most of the previously mentioned factors, which stimulate osteoclasts, do so by upregulating the expression of RANK mRNA in osteoblasts/stromal cells, which will then express RANKL on their cell membranes (25,27). Osteoclast precursors from the monocyte/macrophage lineage express the receptor RANK, and will differentiate into mature activated osteoclasts, when they are exposed to RANKL through cell-to-cell interaction with osteoblasts/stromal cells in the presence of colony-stimulating factor (M-CSF) as well as some other biological activity that has been recently identified (25). This activity has now been characterized with the discovery of three new family members of the TNF ligand and receptor signaling system, which have been shown to play a critical role in the control and regulation of bone turnover (26–30). These include the receptor activator of nuclear factor (NF)-κB ligand (RANKL) (29,30), its receptor, (RANK) (27,31), and its decoy receptor osteoprotegerin (OPG) (28,32). These three molecules appear to be the molecular mediators of osteoclastogenesis and provide a common pathway mediating the activation of bone resorption and controlling physiological bone turnover (Fig. 3).

Fig. 3. Osteoclast commitment and differentiation are regulated by the expression of three critical molecules, macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor (NF)-κB ligand (RANKL), and osteoprotegerin (OPG). Cells of the osteoblastic lineage play a paracrine role in the regulation of osteoclast formation and function. (A) The factors, which stimulate osteolytic bone resorption (e.g., parathyroid hormone [PTH], parathyroid hormone-related protein promoter [PTHrP], vitamin D3, interleukin [IL]-1, IL-6, tumor necrosis factor [TNF], and prostaglandins), interact with receptors on osteoblast/stromal cells stimulating the expression of M-CSF and RANKL. (B) M-CSF is a secreted protein, which interacts with its receptor on monocyte/macrophage progenitors causing these cells to become committed to the osteoclast lineage, creating a pool of osteoclastic precursors. RANKL is expressed on the cell membranes of osteoblasts/stromal cells. (C) When osteoclast precursors, which express the receptor RANK, are exposed to RANKL through cell-to-cell interaction with osteoblasts/stromal cells, they will differentiate into mature activated osteoclasts. RANKL can also bind with OPG, which is a soluble receptor for RANKL, and acts as a decoy in the RANK–RANKL signaling system to inhibit osteoclastogenesis. M-CSF, RANKL, and OPG appear to be the molecular mediators of osteoclastogenesis, and provide a common pathway mediating the activation of bone resorption and controlling physiological bone turnover. The ratio of RANKL:OPG is an important determinant of osteoclast formation and activity and directly determines the rate of both physiological and pathological osteoclastic bone resorption.
M-CSF (27,28). RANKL can also bind with OPG, which is a soluble receptor for RANKL and acts as a decoy in the RANK–RANKL signaling system to inhibit osteoclastogenesis (32). The ratio of RANKL:OPG is an important determinant of osteoclast formation and activity in vivo and directly determines the rate of bone turnover (28). The process of the recruitment and differentiation of osteoclasts is shown schematically in Fig. 3.

During the process of resorption of bone, mitogenic growth factors stored within the matrix are released into the local microenvironments (22–24). These osteoblast-derived growth factors, synthesized as a part of the extracellular matrix, function to regulate the proliferation of osteoprogenitor cells, causing them to differentiate into mature functional osteoblasts. These osteoblasts synthesize new bone matrix, replacing the bone that was lost through resorption, assuring a balance in skeletal remodeling (Fig. 2 [33]).

3. THE BIOLOGY OF METASTATIC DISEASE

In order for a tumor to metastasize, the cells must have the capacity to escape the primary site, travel via the circulatory system, and establish disease at a new distant site. To accomplish this formidable feat, a number of important molecular steps must take place, and this process is remarkably similar for the vast majority of different tumor types with the capacity for metastasis (34).

The pattern of spread of metastasis is dependent both on the regional venous drainage of the primary organ, as well as selective characteristics of the target tissue resulting in homing of tumor cells to these preferential sites (35). The propensity of tumors arising in the breast, prostate, and lung for bony metastasis suggests that there is selective homing of these tumor cells to the skeletal microenvironment. However, a comparison of prostate, breast, and lung tumors shows differences in the distribution of bony metastases, which are most likely explained by different patterns of regional venous drainage (36,37). The high incidence of the spread of prostate cancer to the axial skeleton is partially explained by the drainage of Batson’s plexus, where connections between the vertebral venous plexus and the marrow spaces allow metastases from prostate cancer to spread preferentially to the lower vertebrae (36–38). This suggests that specific biological characteristics of the metastatic site and patterns of blood flow from the primary organ play a role in distant spread of disease. Additional evidence supporting this concept comes from animal model studies where the route of administration of tumor cells influences the occurrence of bone metastases (39). Intracardiac injection of tumor cells has been shown consistently produce skeletal metastases in a number of animal models, whereas intravenous or subcutaneous injection does not produce bony lesions (39–41). Other important biological factors for the dissemination of a malignancy involve angiogenesis, cell adhesion, invasion, and growth factors produced by tumor and host cells, as well as the local environment of the metastatic site (34).

3.1. ANGIOGENESIS

A strong correlation has been observed between tumor aggressiveness and the degree of vascularization of a number of different types of cancers, including breast and prostate (42–45). This data suggests that the capacity of a malignancy to generate new blood vessels (tumor angiogenesis) is important both in progressive growth of the primary tumor and its ability to form metastases (46). A rich vascular bed not only increases the supply of nutrients to the primary tumor, but also increases the likelihood for dissemination. These newly formed vessels are, in all probability, more permeable to tumor cells facilitating entrance into the circulation (47).

The balance between stimulatory and inhibitory growth factors regulates tumor angiogenesis, and a number of studies have demonstrated that metastatic potential directly correlates with tumor cell expression of several gene products, which function as pro-angiogenic molecules (48). These factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor, IL-8, type IV collagenase (matrix metalloproteinases [MMP]2 and MMP9), and others (34,47). The production of these growth factors leads to tumor growth and causes a concomitant increase in vascularization through stimulation of endothelial cell proliferation and migration, as well as a breakdown of extracellular matrix (34). The proteolytic activity of type IV collagenase facilitates the migration of endothelial cells through the altered extracellular matrix toward the source of the angiogenic stimulus (34,47,48). The expression of VEGF in Dunning prostatic adenocarcinoma has been shown to correlate with microvessels density and metastatic potential, where the highest mRNA and protein levels for VEGF were expressed by the most highly metastatic cell lines (49). Recent studies have demonstrated that the pleiotropic transcription factor NF-kB regulates the expression of multiple genes including IL-8 and MMP-9, and is constitutively activated in prostate cancer cells (48). The blockade of NF-kB in the highly metastatic PC-3M human prostate cancer cell line resulted in significant inhibition of VEGF, IL-8, and MMP-9 with subsequent inhibition of angiogenesis, invasion, and metastasis, in both cell culture and in animal models (48). Additionally, angiogenesis in a metastatic focus probably plays a role in the establishment of tumor cells at sites of secondary disease. In an animal model of breast cancer, bone metastases contained large numbers of newly formed blood vessels at the periphery and within tumor tissue (50). In cell culture studies, breast tumor cells stimulated proliferation, migration, and differentiation of bone marrow–derived endothelial cells (50). Cytokine-stimulated endothelial cells may also participate in the establishment of a metastasis and help mediate bone destruction by targeting osteoclast precursors to sites of active bone resorption (51).

3.2. CELL ADHESION

The establishment and subsequent growth of metastatic tumor cells in bone is also dependent on attachment to specific extracellular matrix components and to other cells (endothelial and stromal) in the skeletal microenvironment. Cell adhesion molecules (CAM) mediate several important cell-to-cell and cell-to-extracellular matrix interactions (52,53). These attachments, through specific matrix binding, may signal tumor cell localization, migration, and proliferation and may also induce local expression of cytokines that stimulate bone resorption (24,53).

A category of CAMs, the integrins, has been seen to play an important role in the metastasis of tumor cells to bone (34). Integrins are a family of transmembrane receptors that bind to
a variety of extracellular matrix proteins, are involved with cellular signal transduction and may be critical for the attachment of tumor cells to extracellular matrix (53,54). The αvβ3 integrin, which mediates osteoclastic recognition and attachment to bone matrix, is also highly expressed in bone-residing breast carcinoma cells (55). Integrins interact with matrix through the Arg-Gly-Asp (RGD) peptide sequences present in extracellular matrix proteins (34). The addition of RGD peptides that compete with matrix constituents for integrin binding has been shown to inhibit metastasis of melanoma cells (56). Tumor cell attachment to vascular endothelium and to matrix constituents, such as laminin and fibronectin, are integrin-mediated (52). These proteins underlie endothelial cells and this binding may be an important initial step in tumor cell colonization of a metastatic site (53). Synthetic antagonists to laminin inhibit osteolytic bone metastasis formation by A375 cells in nude mice (57), supporting a role for matrix interactions in the establishment of tumor cells in the skeleton. The integrin α4β1 mediates cell–cell and cell–matrix interactions through adhesion to vascular cell adhesion molecule (VCAM)-1 and fibronectin (58). Transfection of Chinese hamster ovary cells with α4β1 resulted in bone and pulmonary metastases, whereas α4β1 negative cells yielded only pulmonary metastases (58). Antibodies against α4 or VCAM-1 inhibited bone metastasis, suggesting that α4β1 expression, can influence tumor cell trafficking and retention in skeletal tissues (58).

In addition to mediating the retention of tumor cells in bone, matrix interactions may also alter the cells’ biological behavior, favoring proliferation and growth at the metastatic site (59). Bone extracts promote increases in chemotaxis and invasive ability of bone metastasizing prostate and breast cancer cells, but not that of non-bone metastasizing tumor cells (60). Exposure of certain types of tumor to growth factors that are found in the bone microenvironment might enhance their ability to adhere to bone matrix. Treatment of osteotropic PC-3 human prostatic carcinoma cells with transforming growth factor (TGF)-β (which is abundant in bone matrix and released in active form by osteoclastic resorption), causes an increase in synthesis of αvβ1 integrin and promotes the adhesion and spreading of PC-3 cells on bone-derived collagen (24,61).

### 3.3. INVASION

The ability of tumor cells to invade tissues, with transversal of the extracellular matrix as well as angio-lymphatic channels, are critical early steps in the development of metastatic disease, and requires local proteolysis of matrix proteins and cell migration (62). The proteolytic breakdown of constituents of the extracellular matrix facilitates invasion and requires expression of specific proteases. The production of proteolytic enzymes aid tumor cells with detachment from the primary site, invasion of adjacent stroma, entrance and exodus from the circulation, and the establishment at a distant focus. The MMPs are a large family of proteolytic enzymes that are involved with the cleavage and turnover of many different components of the extracellular matrix and play an important role in physiological matrix remodeling (63). A large number of soluble MMPs have been characterized, which can be divided into three groups, including collagenases, stromelysins, and gelatinases, based on their in vitro substrate specificity (63). The production of MMPs by many different tumor types has been demonstrated, and their expression levels have been shown to correlate with invasion, metastasis, and poor prognosis in several human cancers (34,64). Transfection of nonmetastatic cells with specific MMPs will produce a metastatic phenotype, and pharmaceutical agents, which act as specific MMP inhibitors, have been shown to inhibit metastasis in a number of animal models (64–67). In addition to playing a role in tumor invasion by facilitating extracellular matrix degradation, MMPs, through their proteolytic activity, may also help to maintain a microenvironment, which promotes tumor growth (63).

TNF-α is a key regulatory molecule in matrix catabolism, including the stimulation of osteoclastic bone resorption through the RANK–RANK-ligand signaling pathway (68). A number of different types of tumors have been shown to produce TNF-α, and its secretion by tumor cells is dependent on MMP activity (69). The inhibition of MMPs prevents activation and release of TNF-α from the plasma membrane of cells and results in a concomitant decrease in TNF-transcription and translation (70). Because TNF-α has been shown to increase the expression levels of MMPs (71), a vicious cycle could be set up where TNF-α stimulates MMP expression resulting in further TNF activity. This would simultaneously enhance tumor invasion and bone resorption, thus aiding in the establishment metastatic disease in the skeleton.

Tissue inhibitors of metalloproteinases (TIMPs) are produced by nearly all known cells that produce MMPs, bind with MMPs forming inactive complexes, and thus participate in the regulation of proteolysis and matrix turnover (72,73). These inhibitors, in addition to their physiological roles in the balance of matrix degradative activity, appear to be important as regulators of metastases (34). Transfection of metastatic cells with TIMPs or treatment with exogenously added TIMP has been shown to inhibit metastatic disease, including the development of osteolytic bone lesions (64,74,75).

Tumor invasion may involve the direct production of MMPs by tumor cells or, alternatively, induction of proteolytic enzyme expression by the host (52). Host fibroblasts and stromal cells associated with some invasive breast cancers express a gene that encodes stromelysin-3 (76). Stromelysin-3 RNA was found in 95% of invasive breast cancers, however, stromelysin protein and RNA were detected in the fibroblastic cells immediately surrounding the tumor, but not in the carcinoma cells or in stroma at a distance from the lesion (77).

### 3.4. THE ROLE OF GROWTH FACTORS IN TUMOR ESTABLISHMENT AND PROLIFERATION IN METASTATIC SITES

The establishment of metastatic disease requires tumor cell proliferation at the new site. Tumor cell products can impact the local environment of a metastasis in a reciprocal fashion, leading to a growth advantage in selective tissues. Such mechanisms appear to play a role in the case of metastatic disease to the skeleton. The microenvironment of the bone contains a rich supply of mitogenic growth factors (fibroblast growth factors 1 and 2, insulin-like growth factors (IGF)-1 and IGF-2, numerous bone morphogenetic proteins, TGF-β3, and others). These factors are stored within bone matrix and released by osteoclastic resorption (22–24) (Fig. 2). These osteoblast-derived growth
3.5. THE INTERACTION OF METASTATIC TUMOR CELLS WITH OSTEOCLAST

Tumor cells utilize a number of different strategies to stimulate osteoclastic resorption, tipping the balance in normal bone remodeling in favor of bone destruction. By far, the most important of these mechanisms involves tumor cell production of factors that stimulate osteoclastic differentiation and activation. A number of different cytokines and growth factors capable of stimulating bone resorption by osteoclasts are expressed by metastatic as well as primary tumors of the skeleton. The list of factors includes most importantly, PTHrP (81,82), prostaglandin E (83), IL-1, IL-6, IL-11 (84–87), and TNF-α and - (85,86,88). The activated osteoclast may participate in its own regulation in an autocrine/paracrine fashion by constitutively expressing pro-resorptive cytokines and, therefore, pathologically bone lesions with large numbers of active osteoclasts may be, to a degree, self-perpetuating (85,86).

3.6. THE ROLE OF PTHrP

PTHrP is an autocrine/paracrine growth factor and a tumor product, which is homologous with the first 13 amino acid of PTH (89). This molecule shares a common receptor with PTH, was first identified for its role in hypercalcemia of malignancy, and, like PTH, is a potent activator of osteoclastic activity (89–91). PTHrP stimulates osteoclastic bone resorption by increasing osteoblast production of RANK-ligand and decreasing osteoblast production of OPG, thereby tipping the balance of bone remodeling to favor bone breakdown.

3.6.1. PTHrP and Breast Cancer

Clinically, PTHrP has long been suspected to play a causal role in breast cancer-mediated osteolysis. In vivo studies have shown that breast cancer cell lines expressing PTHrP frequently metastasize to bone in nude mice (82). PTHrP is expressed in 50 to 60% of cases of human primary adenocarcinoma of the breast, and these patients are more likely to develop bone metastases (90,92). Of particular interest is the fact that PTHrP expression in bone metastases from breast cancer patients is higher than in the primary tumor, suggesting that the bone microenvironment has somehow enhanced tumor cell production of this factor (92–95). In an elegant series of experiments using an animal model of breast cancer metastasis to bone, it was shown that TGF- released from bone by osteoclast resorption may feedback, and in a paracrine fashion upregulate PTHrP expression by the metastatic lesions in the skeleton (96). In vitro studies demonstrated that TGF- significantly increased PTHrP production by human MDA-MB231 breast carcinoma cells (96). TGF- signaling blockade using a dominant-negative mutant of the TGF- type II receptor, rendered the cells unresponsive to this TGF- effect in vitro, and likewise, the signaling blockade also cause significantly less bone destruction and formed fewer tumors in bone in an in vivo animal model (6,96). This intriguing data suggests that tumor cell stimulation of osteoclastic bone resorption by PTHrP, with subsequent release of TGF- can provide positive feedback, stimulating further production of PTHrP by tumor cells, setting up a paracrine loop with the resultant osteolysis associated with metastatic breast carcinoma (Fig. 4).

3.6.2. PTHrP and Prostate Cancer

The role of PTHrP in skeletal metastases from carcinoma of the prostate is less apparent. Although prostate cancer is characterized by metastases that are osteoblastic, histological and biochemical studies indicate an increase of both bone resorption and bone formation in these lesions, suggesting that the interactions between tumor cells and the bone microenvironment are quite multifaceted (97–100). Despite this, it seems clear that the stimulation of osteolysis is an important, and most likely, necessary component for the establishment of metastatic prostate cancer in bone (39). PTHrP is expressed and secreted by both normal and neoplastic prostate epithelial cells, and a number of studies have provided evidence suggesting a role for PTHrP in the development of bone metastases (101–104). However, this association is complex and appears to be different from the observed role of PTHrP in breast cancer dissemination to the skeleton. PTHrP expression has been demonstrated in a number of prostatic carcinoma cell lines (105). However, transfection of a PTHrP expression vector into the rat
prostate carcinoma cell line MATLyLu was not associated with any difference in the incidence of bone metastasis, size of metastatic foci, or tumor cell proliferation in an animal model (106). Likewise, PTHrP protein was found to have a lower expression in the bone metastases than in the primary prostate tumor in human studies (107), which is in contrast to the observations in breast carcinomas (92–95). In vivo studies have shown that PTHrP expression does have a positive influence on prostate tumor growth and size when these cells were placed in the soft tissues of a rat hind limb, and also protected cells from apoptotic stimuli (105).

### 3.7. RANK–RANKL SIGNALING PATHWAY: RELATIONSHIP TO PROSTATE AND BREAST

Recent reports have provided new insights into alternative molecular mechanisms whereby prostate carcinoma cells may directly mediate osteolysis. In vitro studies have shown that prostate tumor cells are capable of directly inducing osteoclastogenesis from osteoclast precursors in the absence of underlying bone stroma (108). The malignant prostate cells were shown to produce a soluble form of RANKL, which accounted for the tumor-mediated stimulation of osteoclast formation (108). Additionally, in vivo studies demonstrated that administration of OPG completely prevented the establishment of metastatic lesions in bone, emphasizing the important role that osteoclast activity plays in the establishment of skeletal metastases in cancer of the prostate (108). Studies in human tissues have demonstrated the production of RANKL and OPG mRNA and protein in normal prostate and prostate cancer (109), providing additional data supporting the concept of direct modulation of bone turnover. Of interest is the fact that RANKL and OPG expression was significantly increased in all of the bone metastases from prostate cancer compared with nonosseous metastases or the primary tumors in these studies (109).

The significance of RANKL expression in the prostate gland is unclear at this time, but it seems likely that the RANK–RANKL signaling pathway will undoubtedly be found to play some role in normal prostatic physiology. Of interest in this regard is the fact that transgenic mice, which lack RANKL or RANK, demonstrate a mammmary gland defect with the failure to form lobulo-alveolar mammary structures during pregnancy, resulting in the death of newborns (110). RANKL–rescue experiments showed that RANKL acted directly on RANK-expressing mammary epithelial cells (110). These findings suggest that this signaling pathway, which serves such a critical role in the regulation of bone remodeling, is also essential for normal mammary gland development. Further study will be needed to unravel the complex inter-relationships between the breast, prostate, and the skeletal system. However, it seems likely that such investigations will lead to new and novel paradigms in mammary and prostate glandular development and neoplasia, as well as an evolutionary rationale for the complex interactions and inter-relationships between hormonal regulation, gender, and the musculoskeletal system (110).

### 3.8. ESTROGEN RECEPTOR AND BREAST CANCER METASTASIS TO BONE

The hormone estrogen is a mitogen for breast tumor cells that express estrogen receptor. A role for estrogen in the dissemination of these carcinomas to the skeleton has been suggested, but the mechanism remains unclear (6). For patients with cancer of the breast, bone metastasis is involved in nearly 50% of all distant recurrence events (111). A higher rate of bone metastases is seen in lymph node positive compared with node negative patients, and, suprisingly, estrogen receptor positive tumors demonstrated a higher rate of bone recurrence than estrogen receptor negative carcinomas (112–115). This is despite the fact that estrogen receptor positive patients have a lower overall rate of distant recurrence, and a better prognosis compared with estrogen receptor negative tumors (115,116). Additionally, it seems likely that estrogen receptor signaling plays some role in bone metastasis, given that tamoxifen, an estrogen receptor antagonist, has been shown to help reduce bone recurrences in clinical studies (112). The mechanism of this effect may be mediated at least in part by estrogen regulation of PTHrP expression. Estrogen has been shown to regulate the levels of PTHrP in early gestational tissues, as well as increase PTHrP expression in the estrogen receptor-positive breast carcinoma cell line MCF-7. Whether estrogen plays a role in enhanced PTHrP expression in the bone microenvironment remains unclear, but the clinical importance of these observations merits additional investigation, and it may enhance our understanding of tumor-induced osteolysis.

### 4. THERAPY FOR PATIENTS WITH METASTATIC BONE DISEASE

The development of enhanced methods for early detection along with better local treatment, has led to an improvement in outcome for many patients diagnosed with cancer. However, the treatment of patients who develop metastatic disease remains limited and, in many cases, palliative, despite the extensive use of radiation and chemotherapeutic agents. New or novel strategies that delay or prevent the development of metastatic disease would afford an opportunity to significantly improve both the quality and length of life for many patients diagnosed with a malignancy.

It seems clear that the resulting bone damage in metastatic disease to the skeletal system is because of osteoclast bone resorption. Given that the rate-limiting step in bone destruction is the osteoclast, inhibiting the activity of these cells seems to be a reasonable primary therapeutic objective. Thus, the insights that have been gained in our understanding of osteoclast and bone biology have led to the development of new therapeutic approaches in the treatment of metastatic bone disease (3). Effective anti-bone-resorptive agents are currently available, and continue to be developed, for the treatment of these patients.

Osteoclasts are inhibited by a class of drugs known as bisphosphonates, which are analogs of pyrophosphate, with a carbon atom replacing the oxygen and a variety of different side chains (3). By inhibiting the osteoclast, bisphosphonates have been shown to reduce bone resorption regardless of cause. Thus, they have proved to be beneficial in the treatment of a number of conditions characterized by pathological bone loss including metastatic disease, osteoporosis, and inflammatory disorders like rheumatoid arthritis.

A number of clinical studies, as well as investigations in animal models, have documented the efficacy of bisphosphonates for the treatment of skeletal metastases in both breast and pros-
tate cancer (3). Through their inhibition of osteoclastic activity, possibly by inducing osteoclast apoptosis (20), there appears to be a reduction in the skeletal events with bisphosphonate therapy, i.e., pain, fracture, and hypercalcemia, in patients with metastatic cancer. Despite what appears to be a clear benefit with bisphosphonate therapy, better treatments are still needed for patients with metastatic bone disease. Such improvements will most likely come with the development of new pharmacological agents that inhibit osteoclast function.

5. CONCLUSIONS

It is clear that the molecular mechanisms involved in osteolytic metastatic disease are multifaceted and complex involving bidirectional interactions between the metastasizing tumor cells and the bone microenvironment. What has emerged from the study of this process is a central role for the production of factors by specific bone-seeking tumor cells, which facilitate recruitment and activation of osteoclasts, leading to bone resorption, loss of matrix, and bone destruction. The subsequent release of mitogenic growth factors from the matrix would prove to be advantageous by altering tumor cells’ behavior, aiding in their retention and colonization of the bone. These reciprocal interactions could, in turn, set up a series of vicious cycles promoting the proliferation, adhesion, and invasion of cancer cells, as well as further bone resorption, supporting the establishment and progression of skeletal metastatic disease. The hope is that with a better understanding of the molecular mechanisms that mediate the loss of bone, more effective treatments will emerge, and ultimately, we will be able to prevent this devastating complication in patients with common malignancies who develop metastatic carcinoma.

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1. INTRODUCTION

The American Cancer Society estimated that more Americans than ever, 1.33 million, were diagnosed with cancer in 2003 (1). Reportedly, metastases develops in two-thirds of cancer patients (2). After the lung and liver, the skeletal system is the third most common site of cancer metastasis (3). These cancer metastases are also the most common skeletal tumors seen by orthopaedists, and the ratio of metastatic lesions to primary bone tumors is 25:1 (4,5). Delamarter et al. (6) reported that only 29 (1.5%) cases had primary neoplasms of the lumbar spine in their study of 1971 patients with neoplastic disease. The prevalence of metastases increases with age. Patients who are 50 yr or older are at greatest risk for the development of metastatic disease. The gender ratio varies for each type of malignancy. However, when all neoplasms with the potential to metastasize are considered, men and women are equally at risk for metastatic lesions.

Sixty percent of all skeletal metastases (7) and 36% of vertebral lesions are asymptomatic (8) and discovered incidentally. Symptomatic spinal cord involvement has been estimated to occur in 18,000 patients per year (9). Brihaye et al. (10) reviewed a total of 1477 cases and concluded that 16.5% of spinal metastases with epidural involvement arose from the breast, 15.6% from the lung, 9.2% from the prostate, and 6.5% from the kidney. The primary lesion remained unknown in 12.5% of patients. Metastatic lesions were seen in most patients between 50 and 60 yr of age, and there was no difference with regard to gender of the patient. They also analyzed 1585 cases of symptomatic epidural metastases and reported that 70.3% of the patients had involvement of both the thoracic and thora-
columbar regions of the spine, 21.6% had involvement of the lumbar and sacral regions, and 8.1% had involvement of both the cervical and cervicothoracic regions. Their findings confirmed that, although the lumbar spine is more frequently involved with metastatic disease, most patients with neurological dysfunction present with thoracic lesions.

Metastatic lesions in the spine represent the most common site of skeletal involvement (11–15). This chapter focuses on the pathophysiology of tumor growth in the spine with particular consideration of tumor biology in the treatment of spinal metastases.

2. SPINAL METASTASES FROM VARIOUS TYPES OF CANCER

Skeletal metastases are produced by almost all forms of malignant disease, but are most often secondary to carcinomas of the breast, lung, prostate, or kidneys and less frequently from thyroid or gastrointestinal carcinomas (8,9,16–21). The time interval between occurrence of the primary and spinal metastases varies according to the type and site of the primary tumor. In a review of 322 patients with documented metastatic bone disease, Schaberg and Gainor (8) determined that 80% of skeletal metastases arise from four major types of carcinoma (breast, lung, prostate, and renal cell). Breast cancer is the most common source of bony metastasis in women. Between 65 and 85% of women with breast cancer develop skeletal disease before death (22). Among men, metastases from bronchogenic and prostatic carcinomas occur with the greatest frequency. Lymphoma and multiple myeloma are also a common source of disseminated skeletal lesions. However, there is some debate about whether multiple myeloma and lymphoma are considered metastatic or primary lesions of bone. Black et al. (9) estimated that for 9% of spinal metastases the primary source of the tumor could not be determined.
3. WAYS OF SPREADING: ANATOMICAL FACTORS

3.1. PAGET VS EWING

Two apparently opposing theories of patterns of tumor spread have long been discussed. In 1889, the English surgeon Stephen Paget published his observations from 735 autopsies of breast cancer patients. He noted that metastases were found more frequently in the liver and brain than in other organs, such as the kidneys and spleen. This led him to formulate the “seed and soil” hypothesis, which states that the process of metastatic spread depends on “cross-talk” between selected cancer cells (the “seeds”) and specific organ microenvironments (the “soil”) (23). In 1928, James Ewing, an American pathologist, countered that there was no need to invoke mysterious “soil conditions,” but that patterns of blood flow carrying cells from the primary tumor could account entirely for the unequal distribution of metastases. Hence, the first organ encountered in the circulation would harbor the greatest number. The observation that the lung, which was the first organ traversed by most breakaway tumor cells, has a high incidence of metastases supported this “mechanical” hypothesis (24). In recent years, researchers have come to appreciate that both Paget and Ewing were partly correct, but neither hypothesis is thought to be entirely correct because predisposition to metastatic seeding is most probably multifactorial (25).

Others have hypothesized that tumor cells lodge at sites of trauma, possibly attracted by a tumor growth-promoting factor released by dead or dying cells (26). It has been observed that the vertebral body trabeculae routinely develop microfractures (27), which may provide the microenvironment necessary for metastatic seeding. The host responds by producing bone in an attempt to repair the injury produced by the cancer invasion. Fast-growing aggressive lesions are associated with minimum reactive bone and radiographically appear purely lytic. Slow-growing or less aggressive metastases allow the formation of reactive bone to various degrees and appear radiographically blastic. Mixed areas can occur either within a single metastasis or at different sites (28–31).

3.2. ROUTE OF SPREAD FROM THE PRIMARY SITE TO THE SPINE

Principle characteristics of malignant neoplastic lesions are the growth of tumor cells distant from the primary lesion. These distant lesions are referred to as metastases and are commonly found in the skeletal system. There are four potential pathways of metastasis: venous, arterial, direct extension, and lymphatic. It is thought that the most common pathway for metastatic embolization to the spine is through the venous system. To become established in the medullary canals of the spine, tumor emboli must first go through the capillary beds of the liver and lungs, often by establishing a metastasis at these locations. Alternatively, the tumor emboli may circumvent these filters and reach the medulla sinusoids by an entirely different route.

3.2.1. Venous Spread

After blood enters the vertebral body, it is drained by a large central basivertebral vein and smaller paraarticular veins (32). Under normal conditions, 5 to 10% of the blood within the portal and caval systems is shunted into the vertebral venous system (33). These venous channels connect with the epidural venous plexus, a valveless system of veins within the spinal canal, first suggested to be a potential source of metastatic embolization by Batson (34,35). Batson’s plexus is a network of veins located in the epidural space between the bony spinal column and the dura mater covering the spinal cord. It is connected to the major veins that return blood to the heart and the inferior and superior vena cava. This plexus of vein is unique because there are no valves to control blood flow, and therefore any increased pressure in the vena cava system results in increased flow backward into Batson’s plexus (Fig. 1).

In 1940, Batson (34) performed cadaveric studies in which he injected dye into either the penile dorsal vein of male specimens or the breast veins of female specimens. He discovered that the dye could be recovered in the vertebral veins. He postulated that any increase in intra-abdominal pressure would divert blood into the epidural venous plexus, thus providing a potential pathway of vertebral metastatic embolization for breast and prostate cancers (34). The tendency of bone, and the axial skeleton in particular, to be a frequent site of skeletal metastases may be explained, at least in part, by the presence of Batson’s plexus. Coman and Delong (36) provided additional evidence by first injecting tumor suspensions into the femoral veins of rats and then sacrificing the animals to determine the areas of embolization. They discovered that lung embolization occurred in 15 of 16 animals. When the same experiment was performed while the animal’s intra-abdominal pressure was artificially increased, lumbar vertebral embolization developed in 12 of 14 animals. This provided in vivo evidence that Batson’s epidural venous plexus is a potential pathway of metastatic embolization to the vertebral column.

3.2.2. Arterial Spread

Arterial embolization is another way of metastatic spread to the spine. Tumor cells may embolize through the arterial system and enter the vertebral bodies through the nutrient arteries.
For example, tumors of the lung may seed the vertebral column directly through the segmental arteries. This is believed to be another common mechanism of metastasis in lung cancer (37).

### 3.2.3. Direct Extension

Direct extension has also been suggested as a potential pathway for prostate cancer (38). Tumors located in either the retroperitoneum or the mediastinum may directly erode into the vertebral bodies as they expand, or they may enter the spinal canal through neural foramina. This explains why a prostate cancer metastasizes more often to the lumbar spine, whereas lung and breast cancers metastasize more often to thoracic spinal lesions.

#### 3.2.4. Lymphatic Spread

Another route of metastatic spread to the spine is lymphogenous metastasis. Although lymphangiography has demonstrated lymph channels within bone, their clinical significance in providing a pathway for spinal metastatic embolization has not been defined.

### 3.3. SPINAL LEVELS OF DIFFERENT TYPES OF CANCER

Approximately 70% of symptomatic lesions are found in the thoracic spinal region and 20% in the lumbar region. Jaffe et al. (39) demonstrated that more than 70% of patients succumbing to cancer had evidence of vertebral metastases after careful postmortem examination. In his series, the thoracic spine was the most commonly involved segment of the vertebral column. Other investigators (35,40,41) have found that the lumbar spine was more frequently involved. Metastatic lesions affect the cervical spine less frequently than other portions of the axial skeleton (10%). Many large studies of metastatic disease of the spine do not include the cervical spine. One could argue that this is because of the relatively low incidence of cervical metastatic lesions (42–44). More than 50% of patients with spinal metastases have multiple level involvement. Approximately 10 to 38% of patients have multiple, noncontiguous segment involvement. Gilbert et al. (45) found that tumors of the breast and lung usually metastasized to the thoracic area. However, the entire spine is often involved. Prostate carcinomas usually metastasize to the lumbar spine, sacrum, and pelvis (45).

Venous drainage from the breast by the azygos veins communicates with the paravertebral venous plexus (Batson’s plexus) in the thoracic region, and the prostate drains through the pelvic plexus in the lumbar region (35). Retrograde flow through Batson’s plexus has been shown to occur during Valsalva’s maneuver and may allow direct implantation of tumor cells in the vascular sinusoids of the vertebral body without passing through the usual capillary networks. By contrast, blood from the lung drains principally via the pulmonary vein into the left heart and showers its tumor cells in a generalized fashion throughout the skeleton. Tumors of the colon and rectum, which drain through the portal system, tend to seed the liver and lung with metastases much earlier and more frequently than they do the axial skeleton.

### 4. PHYSIOLOGY OF SUCCESSFUL IMPLANTATION

For cancer cells to form viable metastatic foci, an exceedingly complex series of events must occur between those cells and the host environment (46–48). The metastatic process is conventionally described as a five-step event: (1) release of cells from the primary tumor; (2) invasion of efferent lymphatic or vascular channels; (3) dissemination of these cells to tissues distant from their source; (4) endothelial attachment and invasion of the new host; and (5) growth of the original colony into a metastatic tumor focus (49–51).

#### 4.1. SEPARATION OF CELLS FROM THE PRIMARY TUMOR

The first stage, separation of tumor cells from the primary tumor, appears to be because of a combination of the loss of intercellular cohesiveness and subsequent transport within the original tumor interstitial tissue enhanced by a local collagen hydrolysis. The production of proteolytic enzymes aid tumor cells with detachment from the primary site and invasion of adjacent stroma. The matrix metalloproteinases are a large family of proteolytic enzymes that play an important role in physiologic matrix remodeling (43). The production of matrix metalloproteinases by many different tumor types has been demonstrated, and their expression levels have been shown to correlate with invasion and metastasis (44,45).

#### 4.2. VASCULAR INVASION

Once tumor cells have escaped their parent they must invade local vessels to spread to distant sites as tumor emboli. Venous penetration appears to play a much more important role than lymphatic infiltration in the development of distant metastases. Spread by the lymphatic system is probably important only as far as the regional lymph nodes are concerned, from there the venous system is the carrier.

#### 4.3. TRANSPORT

Once free in the circulation, cancer cells are able to migrate further depending on the local organ blood flow, general patterns systemic circulation, and perhaps a particular vulnerability of peripheral tissue (such as bone marrow) owing to peculiarities of sinusoidal permeability. The primary factor affecting migration, however, appears to be the ability of those cells to survive within the circulation during transport. Circulating tumor cells appear to be protected in part by a fibrin-platelet coagulum that surrounds the cells (26,52,53). This coagulum isolates the circulating malignant cells from the hostile environment factors of the host, allowing them to multiply in some safety and to produce a small and protected colony (15,54,55).

#### 4.4. HOST ENDOTHELIAL ATTACHMENT

Once tumor cells have reached a peripheral site suitable for the development of a metastatic focus, direct attachment of these cells to vessel endothelium must occur before the tissues of the host organ can be invaded. The tendency of cancer cells to adhere to vascular endothelium is distinct from the mere formation of tumor emboli and provides the basis for establishing “beachheads” before interstitial invasion.

#### 4.5. PROLIFERATION OF A METASTATIC FOCUS

Once a colony of tumor cells has become established within a peripheral site, it may be called a micrometastasis. In spinal metastases, the most common site of colony arrest is in the vascular end-loops adjacent to the vertebral end-plate. However, it will not become a clinically significant tumor focus unless it obtains its own vascular supply (56). Secretion of “a tumor angiogenesis factor” was first demonstrated by Folkman (57). The factor attracts vessels to a small tumor colony that
would remain viable only through local tissue diffusion of nutrients and be incapable of subsequent invasion itself. The production of this angiogenesis factor appears to be blocked in part by postimmune responses, presumably mediated through lymphocytes. This phenomenon explains the late appearance of metastases long after resection of the original tumor focus. In such an instance, it can be postulated that a micrometastasis was established years earlier and attracted the vascularised tissue required for growth much later. Adjuvant chemotherapy is probably most effective against such viable, yet poorly vascularized, peripheral tumor colonies.

In addition to a vascularizing factor, all tumors also appear to be able to secrete specific factors that enhance the establishment of their colonies in particular organs. Breast, prostatic, lung, renal, and thyroid tumors all secrete osteoclast-activating factors that enhance their successful establishment in bone (58).

5. PROGRESSIVE GROWTH

The red bone marrow, located inside vertebral bodies, long bones, and flat bones, has a rich sinusoidal system. Sinusoidal vessels are usually under low pressure, thus allowing for the pooling of blood. This pooling of blood, along with other factors such as fibrin deposits and thrombosis, may encourage tumor growth. The red marrow of bone provides a biochemically and hemodynamically suitable environment for the implantation and proliferation of tumor cells. Because the capillary network of the vertebral red marrow is particularly susceptible to tumor implantation and invasion, tumor cells find it easier to escape from the circulation and multiply within the fine network of cancellous bone (18). The axial skeleton, which contains red marrow throughout a human’s lifetime, is the most common site of skeletal metastasis. Finally, there are intrinsic factors inherent to the tumor cells themselves that may give one cell line a particular advantage in surviving and growing in the medullary space. Specifically, the elaboration of prostaglandins and the stimulation of osteoclast activating factors by breast cancer cells have been associated with the establishment of lytic metastases in bone (59). These cells may also produce a protective fibrin sheath, which further isolates them within the marrow.

After a metastasis is established within cancellous bone in vertebral bodies, it expands by producing a number of substances that either directly or indirectly cause bone resorption (60). Such chemical factors, including parathyroid hormone, osteoclast-activating factor, prostaglandins, and transforming growth factor related to metastases, have an effect on bone mineralization (61–70).

High levels of collagenase appear to correlate with tumor invasiveness, presumably the product of destroyed ground substance of bone (71). Tumor cells have been shown to secrete osteoclast-activating factor, which results in bone resorption through osteoclast stimulation (40,72). Tumors also are often associated with osteoblastic activity (prostate or breast cancers) release factors that stimulate osteoblasts to produce bone (73). Experimental studies involving breast and renal cancer have suggested that osteolysis may also be mediated by tumor prostaglandin secretion (74–76). Indomethacin, a prostaglan-
din inhibitor, has been shown to diminish, but not prevent, bone destruction in rats injected with tumor suspensions (77). In addition, as the neoplastic tissue envelops and applies direct pressure on the bony trabeculae, they become ischemic and are resorbed.

After cancellous bone in vertebral bodies is destroyed by metastases, cortical bone invasion occurs secondarily. This is consistent with the observation that metastatic involvement of a pedicle, which is composed of trabecular bone surrounded by cortical bone, is rarely observed alone, and is usually the result of direct extension from either the vertebral body or the posterior elements (78). Although the initial radiographic finding often will be destruction of a pedicle, the vertebral body typically is the first anatomic part to be affected (79) and is involved 20 times more often than the posterior elements (78) that is seen ranging from 14 to 30% of the cases. This is explained by the fact that in the absence of a blastic or sclerotic reaction from the vertebral cancellous bone, between 30 and 50% of the cortical bone body must be destroyed before these changes can be recognized on a plain X-ray. However, with only minimum involvement, the pedicle exhibits early radiographic cortical changes that can be seen when the pedicle in cross-section is inspected on an antero-posterior radiographs (12). Thompson et al. (80) demonstrated by postmortem examination of patients who had died of metastatic disease that the posterior vertebral elements were significantly involved only one-seventh as often as was the vertebral body. Less often, the epidural space becomes the initial site of metastasis. In rare cases (3.4%), patients with neurological compromise may develop subdural or intramedullary metastases (10).

Each vertebra has barriers to the spread of tumor. The posterior longitudinal ligament is the weakest. Epidural metastasis is the most ominous complication of bone metastasis to the vertebral spine and is a surgical emergency. The most common path for tumor spread is through the posterior longitudinal ligament into the epidural space (81). The tumor enters the epidural space by contiguous spread from adjacent vertebral metastasis in the vast majority of cases. The remaining cases arise from the direct invasion of retroperitoneal tumor or tumor located in the posterior thorax through adjacent intervertebral foramina, or rarely from blood-borne seeding of the epidural space.

Besides mass effect, an epidural mass can cause cord distortion, resulting in demyelination or axonal destruction. Vascular compromise produces venous congestion and vasogenic edema of the spinal cord, resulting in venous infarction and hemorrhage. The relative importance of vascular factors as opposed to purely mechanical ones has been a subject of controversy for many years. The tempo of development of spinal compression is, perhaps, impossible to generalize. Once neurological symptoms become manifest, the condition is a surgical emergency.

6. SIGNIFICANT FACTORS FOR SUCCESSFUL TREATMENT

Treatment of patients with metastatic disease of the spine continues to be a challenging problem. With continued advances in the treatment of primary disease and local recur-
rances, patients are living longer and more frequently require treatment for symptomatic distant metastases. Additionally, the management of metastatic spinal disease has evolved considerably over the last decade, and several classification systems that may assist surgeons in determining appropriate surgical candidates have been proposed (16,62,68,69).

Surgical treatments should be tailored according to the patient’s predicted survival period (1). Tokuhashi et al. (2) proposed an original scoring system for the preoperative evaluation of metastatic spine tumor prognosis. However, their scoring system is only applicable to the decision making between excisional or palliative procedures. Because aggressive surgery, such as total en-bloc spondylectomy, is now being more frequently advocated for spinal metastases, Tomita et al. (3,4) addressed the problem of appropriate surgical candidate selection with a more comprehensive classification system that is based on grouping tumors into intracompartmental, extracompartmental, and multiple lesions. Tomita’s review clearly underlines the need for consideration of general oncological concepts to achieve successful local control of the spine lesion (82–85).

Recent advantages in spinal instrumentation and surgical approaches have enabled spine surgeons to treat these lesions more radically and to reconstruct the spinal column more effectively. The use of spinal stabilization in conjunction with the surgical treatment of these neoplasms has resulted in significant outcome-related improvements. Because significant advances have also occurred in the improved imaging techniques, diagnosis has become more accurate. It is desirable to establish newer ways of early detection of distant metastases to the spine, to predict biological behavior, and finally, to improve clinical management of spinal metastasis.

The inherent nature of specific primary and metastatic neoplasms determines their biological behavior and dictates which will have slow or rapid growth, which will be invasive, and which will produce metastases. Although metastatic lesions usually demonstrate behavior similar to their primary lesions, this is not always true; some metastases may be far more invasive or rapidly growing than the primary lesion of origin. It is this biological behavior of the primary or metastatic lesion that determines the likelihood and rate of spinal cord compression. Rapid tumor expansion may produce vertebral erosion, fracture, and result in acute cord compression with a poorer prognosis for improvement. Improved understanding of the tumor types and their biology will empower the surgeon to better define surgical indications and to predict successful clinical outcomes with surgical resection.

Currently, the treatment options available for metastatic spinal disease include radiation therapy, hormonal manipulation, chemotherapy, surgical resection, and most commonly, a combination of two or more of these treatment modalities. Reports of the success of various treatment protocols are contradictory because there is a lack of a standardized method for evaluating treatment success and there is a lack of understanding of the natural history of the metastatic disease process itself. Thus, current treatment options of patients with metastatic disease to the spine remain limited and in many cases are palliative. Several tumor-derived factors that stimulate bone resorption by osteoclastic activation have been recognized. Examples of such factors are parathyroid hormone related protein (70), prostaglandin E (71), Interleukin-1 (72), and tumor necrosis factor (73). Effective anti-bone-resorptive agents are currently available, and continue to be evaluated for the treatment of bone resorption owing to osteoclast activation (74).

From a surgical standpoint, it is important to consider that metastatic epidural compression in most instances develops ventral to the thecal sac. Therefore, studies describing the results of posterior decompression alone to treat neurological deterioration failed to show significant improvement of neurological deficit with surgical decompression alone. There is no advantage in the use of surgical laminectomy over radiation therapy alone for which reason laminectomy alone for decompression of neural elements has fallen out of favor (2,86–92).

Because of these poor results, many physicians have been taught that surgical intervention is not a viable addition to the treatment armamentarium and should be considered only as a last resort. However, anterior decompression, through removal of the vertebral body and any epidural tumor, has shown great benefit for the patients with spinal cord compression. Anterior surgical intervention is increasingly being accepted as a valuable component of the interdisciplinary treatment approach to the care of patients with symptomatic spinal metastases. Certain tumors (renal cell) with single metastatic foci without vertebral collapse are best treated by extirpation, when possible, and no irradiation, to allow the best long-term survival (46,48).

7. CONCLUSIONS

Despite recent advances in the treatment of spinal metastases, many problems remain making successful management of spinal metastases difficult. Early detection of small metastatic foci plays an important role. We anticipate that future advances in the understanding of molecular and cellular mechanisms in the various stages of carcinogenesis may provide the more effective clues to prevention and treatment of spinal tumors.

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