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**Project Title:** **Factors that Correlate with an Increase in Fracture Risk in Patients Who Have Been Diagnosed with Bony Metastatic Disease**

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| **Study Details** | **Purpose** | **Subjects** | **Outcome Measures** | **Results and conclusions** | **Strengths/Limitations/Notes** |
| **Author/Year:** Yong-Cheng, et. al/20121  **Study Design:** Retrospective review | Explore clinical features of pathological fractures in extremities caused by bone tumors and lesions | 139 patients with pathological fractures were recruited  - 79 males and 60 females with diagnosis of bone tumors or tumor like lesions and pathological fractures located in the long bones | - Differences in fracture forces between groups of bone tumors  -Prodromes between different group of bone tumors leading to fractures | - Highest pathologic fracture morbidity rate 32.3% in the 11-20 year group, 19 fractures in the 40-50 year group, 17 fractures in the 71-80 group  - Before fracture occurred **48.2% had prodromes: 58 patients had pain, 6 had a lump, 2 had soreness and swelling**  - **83.8% of patients had pain at fracture site before injury**  -Osteosarcomas were most common tumors resulting in fractures (72.73%)  - Limb with lesions had pain or soreness when weightbearing | **Strengths:** large sample size, analyzed large cohort of patients consistently treated, found new and important information for orthopedic surgeons  **Limitations:** retrospective review of cases from one institution, number of patients of each type of bone tumor is small and limits ability to draw more credible conclusions |
| **Author/Year:** Benca, et. al/ 20162  **Study Design:** Literature review | Identify all methods for fracture risk evaluation in patients with femoral metastases and their predictive value | - 18 articles were included: prospective and retrospective clinical and/or radiological data, studies on engineering methods in fracture risk assessment, biomechanical studies conducted on human, animal, or artificial bone | - Two independent reviewers reviewed all abstracts of the articles  - Mirels’ scoring system of 1989 | - Currently **lack adequate clinical methods for fracture risk prediction** in patients with femoral metastases  - **Golden standard used today to predict impending fractures- Mirels’ score on scoring system of 1989** but leads to overtreatment and fails to recognize non-impending fractures  - Engineering methods provide high accuracy but need clinical validation and are difficult to adapt to the variable physiological and pathophysiological conditions found in clinical routine  -Lytic lesions have highest impact on bone strength increasing fracture risk  -**Cortical involvement of 50-75% in metastatic long bones and especially over 75% or cortex and likely to fracture**  -**Increasing local pain indicator for lesion with growing fracture risk** | **Strengths:** large sample size, compared golden standard with fracture risk prediction based on engineering methods, acknowledges the lack of a gold standard method  **Limitations:** lower quality evidence used, no control or experimental groups, studies used were over 10 years old, some articles did not have sufficient validity but were included |
| **Author/Year:** Mirels, et. al./ 20033  **Study Design:** Retrospective analysis | Compare accuracy of Mirels’ scoring system to individual risk factors that may be useful in predicting impeding pathologic fractures | 38 patients who had metastatic bone lesions with no fracture or history of fracture and no previous irradiation to the bone | Scoring of the preirradiation roentgenograms was done separately by 3 consultant orthopedic surgeons according to Mirel’s scoring system | - 35% of the lesions sampled fractured within a period of 6 months  - Scores within the fracture group ranged from 7 to 12  - **Most accurate score for diagnosing an impending fracture using this classification system is 9**: chance of fracture is 33% and false positive is 0%; score of 8: suggestive, probability of fracture 15%, false positive is 6%,  - **All patients in study in which pain aggravated by function ended up with a fracture** (p=0.0001)  - Probability of a fracture in a patient with nonfunctional pain is 10%  - Correlation between pain aggravated by function and size of the lesion: **90% of patients had lesion occupying more than 2/3 diameter of bone** | **Strengths:** uses a combination of roentgenographic and clinical risk factors to give each patient a score, scoring completed by 3 orthopedic surgeons to compare to actual outcome, provided reliability data of scoring system, examined each risk factor independently  **Limitations:** Retrospective review of lesions in patients, smaller sample size of participants, data analyzed was older (1981-1985), selectively chose participants files based on known metastatic lesions |
| **Author/Year:** Damron, et. al/ 20034  **Study Design:** Retrospective review | Critically examine the hypothesis that Mirels’ rating system for impending pathologic femur fractures is reproducible, valid, and applicable | - 12 patients with femoral metastatic lesions aged 44-74 years old | - 53 physicians used Mirels’ rating system to assign a score to each patients’ case and then they were asked to predict whether the patient in the case history was likely to have a pathologic fracture  -Measured agreeance between physicians predicted fracture risk based on Mirels’ score | - Concordance analysis for overall scores were highly significant  - **Individual Mirels’ score component that showed greatest variability was pain**  - Sensitivity of Mirels’ system was 91% and specificity was 35%  - Odds ratio in favor of predicting fracture based on Mirels’ assigned scores was 4.56  - **Mirels’ scoring system is reproducible and valid for prediction of impending fracture risk** | **Strengths:** large number of examiners (53) from 5 experience levels to test Mirels’ rating system, determined which group was most effective/least effective at using this as a screening tool, compared using tool to clinical judgement  **Limitations:** not all clinical information usually available to the clinician was provided, small sample size, only assessed patient case histories and radiographs, lesions restricted to femoral involvement, patient case selection was not randomized |
| **Author/Year:** Patel, et. al., 20015  **Study Design:** Literature Review | Review the evaluation of fractures that occur secondary to bone destruction by metastatic cancer and guidelines for estimating fracture risk | 7 retrospective articles with patients who had metastatic bone disease | Risk factors leading to fracture | -**Risk of fracture increases with duration of metastatic disease**  - Radiation increased fracture risk in patients with metastases  -**Pain is a sign of decreased mechanical strength of bone and increased fracture risk**  - 2 studies found that less than half of their patients with fractures complained of pain  - **Patients with >50% cortical involvement developed a fracture**  - Lytic lesions have increased fracture risk | - **Strengths:** large number of articles included for review, used Mirels’ score in addition to certain factors that have been shown to increase fracture risk to improve prediction of fractures in patients  **- Limitations:** review of articles, did not include control vs experimental groups, no statistical data to back up results found, did not include information on sample size or strength of articles reviewed |
| **Author/Year:** Beals, et. al., 19716  **Study Design:** Retrospective Review | Review the incidence of femoral fractures occurring in patients with metastatic breast cancer | 338 patients with metastatic breast cancer | Incidence of femoral fractures | - **Fractures occurred in patients that had lesions greater than 2.5 cm in diameter in the femur** or when a lesion this size was **painful regardless of location**  -**Femoral metastases have highest risk of fracture** (32%) | **Strengths:** Large sample size, reviewed articles from longer time span (1956-1961, 1965-1969)  **Limitations:** Retrospective review, older article, only included patients with metastatic breast cancer |
| **Author/Year:** Dijkstra, et. al./ 19977  **Study Design:** Retrospective Review | Review patients with impending and actual fractures due to metastatic bone lesions in femur and develop a criteria for lesions at risk of fracturing | 54 patients (43 women and 11 men) aged 24-85 years old with 30 impending and 24 actual pathological fractures in subtrochanteric femoral region treated from 1978-1990 | Fracture rate among lesions and factors increasing fracture risk | - **Local pain occurred in 41 patients (78%)** within 14 weeks before fracturing  - One-third of patients with an impending (11/30) or actual (9/24) fracture complained of initial pain within 3 months before surgery  - **5/6 patients complained of aggravating pain that resulted in fracture**  - Pre-fracture pain reported to occur in 11-84% of patients who have fractures  - **Increasing local pain was a predictive factor of an actual fracture occurring within 2 months** | **Strengths:** results correlated with other more recent review studies, looked at actual versus impending fracture to determine fracture risk, review large time span of review studies, included patients with different kinds of metastatic disease  **Limitations:** retrospective review, older article, small sample size, lower quality evidence studies were included |
| **Author/Year:** Sheill, et. al./ 20188  **Study Design:** Narrative review | Examine factors for consideration with exercise prescription in metastatic bone disease, review evidence from trials of exercise prescription in this population, and examine the efficacy and safety outcomes of exercise interventions | - 11 studies were included (7 RCTs, 3 single arm studies, 1 multi-arm interventional study)  - Total of 593 patients were included with metastatic disease as a result of solid primary tumors | - Results of the literature search were screened by 2 authors for inclusion criteria  - Mirels’ classification system  - Fracture rate and factors related to increased risk | - **Steroid use is a strong independent risk factor for fractures**  - **Androgen-deprivation therapy for prostate cancer increases fracture risk by 20-45%**  -Mirel’s classification system for bone fracture risk has good sensitivity (91%) but poor specificity (35%)  -**Pain associated with functional activity is associated with greater risk of pathological fracture**  - **Pain with weight bearing activities can indicate pathological fracture**, especially in lower extremities, therefore, weight bearing should be avoided in the presence of pain | **Strengths:** comprehensive review of evidence from trials of exercise prescription in this population, compared experimental and control groups, large sample size of participants, compared aerobic, resistance, and a combo of both exercise programs  **Limitations:** narrative review, studies involving animal studies were included, some low quality evidence studies were included |
| **Author/Year:** Wang, et. al/ 20159  **Study Design:** Cohort study | Evaluate fracture risk in prostate cancer population treated with ADT, association between different types of ADT and risk of fractures, and understand risk of mortality after cancer | - 25,544 men diagnosed with prostate cancer between 2004-2012 from the New Zealand registry and had treatment using ADT | - Fracture requiring hospitalization | - 1538 (6%) patients experienced at least one fracture that required hospitalization  - Among these patients, 43.3% had a pathological fracture or spinal cord compression  **- Rate of fracture among ADT users was 5.8% with localized disease and 19.6% for patients with locally advanced or metastatic disease**  - **Use of ADT was associated with a significant 2.83x increased risk of any fracture** (OR= 2.83, 95% CI 2.52-3.17) **and of hip fracture**  - Use of bisphosphonates were associated with a significantly increased risk of any fracture (5.89x increased risk with localized disease and 2.03x increased risk with metastatic disease) | - **Strengths:** large sample size, population based cohort of men given ADT, long follow up time  **- Limitations:** majority of patients are not staged, some patients may have cancer registered years after diagnosis, adjusted diagnosis date which could introduce bias, many fractures are not recorded in the system thus fracture risk could be underestimated, lack of data on certain risk factors of fracture such as smoking, alcohol, BMI, use of corticosteroids |
| **Author/Year:** Alibhai, et. al/ 201010  **Study Design:** Matched Cohort Study | To study whether ADT increases nonfragility fracture risk, other clinical variables that increase fracture risk in these patients | **-** 19079 men 66 years old or older diagnosed with prostate cancer between 1995- 2005, received at least 6 months of ADT therapy | - Fracture and fracture requiring hospitalization | - Total of 1778 ADT users (9%) vs 5% of nonusers had a fragility fracture of the spine, hip/femoral neck or other parts of the femur  **- 3387 ADT users (17.2%) had any fracture compared to non-users**  - **ADT was associated with increased fracture risk**  - Other factors that predicted fracture risk: older age, bone thinning drug use, prior fracture, prior osteoporosis diagnosis | - **Strengths:** men in ADT group vs non-ADT group were matched based on age using propensity score based technique with logistic regression model which balanced distribution of possible confounders between patients who did and did not receive ADT, obtained detailed set of covariates for matching and risk adjustment, large sample size, population based cohort of men on ADT, comprehensive linked databases, long follow up  **- Limitations:** limited to studying men 66 years old or older to obtain medication info, degree of under coding of minor fractures since some may not seek medical care, observed few of the various rarer fracture types limiting ability to draw conclusions of ADT based on these outcomes, included men on antiandrogens in cohort, clinical fracture risk factors were not available for inclusion in models |
| **Author/Year:** Shahinian, et. al/ 200511  **Study Design:** Cohort Study | Assess the risk of fracture associated with androgen deprivation therapy in the form of orchiectomy or treatment with GRH agonists | - Records of 50,613 men 66 years old or older having received a diagnosis of prostate cancer in period of 1992 to 1997 and received GRH agonist or underwent orchiectomy within 6 months after receiving diagnosis | - Primary outcomes: any fracture and fracture resulting in hospitalization  - Secondary outcomes: fractures at specific sites and new diagnosis of osteoporosis | - Small but **statistically significant increase in patients with any fracture in the group receiving androgen-deprivation therapy** (19.4% in ADT group)  - Relative risk of occurrence of any fracture increased steadily with the increasing doses of a GRH agonist received during the first year after diagnosis  - 7-16% of fractures in prostate cancer were related to bone metastases | **Strengths:** large sample size, included control group who did not use GRH therapy, matched control vs treatment group for similar characteristics  **Limitations:** did not separate fractures that were related to bone metastases, short time period analyzed with exposure to GRN agonists |
| **Author/Year:** Townsend, et. al., 199712  **Study Design:** Retrospective review | Determine the risk of bone fracture in men receiving luteinizing hormone releasing hormone (LHRH) for prostate carcinoma | 224 patients who were treated for prostate carcinoma between 1988 and 1995 with LHRH injections | Bone fractures | - **15 of 139 patients (11%) with bony metastases suffered a fracture**  - the number of injections did not have a significant difference on the rate of fracture | **Strengths:** large sample size, divided sample size based on extent of cancer and if had malignancy, included the number of injections into the results of risk of fractures  **Limitations:** determined if patient had fracture based on telephone interview with all participants, could not determine stage of disease or if had bony metastases in 43 patients, included fractures from trauma (MVA, fall), did not include statistical analysis data for results, older article |
| **Author/Year:** Klaassen, et. al., 201713  **Study Design:** Retrospective cohort study | Identify risk factors for skeletal related events (SREs) in men with metastatic prostate cancer and is bone pain a strong predictor of time to SRE in these patients | 233 men aged 68-81 years old with metastatic prostate cancer | Time to SRE occurring including fractures and number of SREs occurring | - **Bone pain was found to have a significant increased risk of bone fracture and be the strongest predictor of SRE**  - Radiation therapy as a primary localized treatment increased fracture risk  - Increased number of bone metastases led to increased risk of fracture  - **Statistically significant difference in quicker progression to SRE with patients who had bony metastases and bone pain** | **Strengths:** access to complete medical records which allowed for accuracy in assessing SRE risk, large sample size, performed detailed multivariable analysis  **Limitations:** retrospective design, patients were from 2 veterans affairs hospitals limiting generalizability, 21% of cohort was missing data regarding bone pain, did not use standardized questionnaire to assess bone pain |

Bibliography

1. Hu Y-C, Lun D-X, Wang H. Clinical features of neoplastic pathological fracture in long bones. *Chin Med J* 2012;125(17):3127-3132.

2. Benca E, Patsch JM, Mayr W, Pahr DH, Windhager R. The insufficiencies of risk analysis of impending pathological fractures in patients with femoral metastases: A literature review. *Bone Rep.* 2016;5:51-56. doi:10.1016/j.bonr.2016.02.003.

3. Mirels H. Metastatic Disease in Long Bones A Proposed Scoring System for Diagnosing Impending Pathologic Fractures. *Clin Orthop Relat Res* 2003;415S:S4-S13.

4. Damron TA, Morgan H, Prakash D, Grant W, Aronowitz J, Heiner J. Critical evaluation of Mirels’ rating system for impending pathologic fractures. *Clin Orthop Relat Res* 2003;(415 Suppl):S201-7. doi:10.1097/01.blo.0000093842.72468.73.

5. Patel B, DeGroot H. Evaluation of the risk of pathologic fractures secondary to metastatic bone disease. *Orthopedics* 2001;24(6):612-7; quiz 618.

6. Beals R, Lawton G, Snell W. Prophylactic Internal Fixation of the Femur in Metastatic Breast Cancer. *Cancer* 1971;28(5):1350-1354.

7. Dijkstra PDS, Oudkerk M, Wiggers T. Prediction of pathological subtrochanteric fractures due to metastatic lesions. *Arch Orthop Trauma Surg* 1997;116:221-224.

8. Sheill G, Guinan EM, Peat N, Hussey J. Considerations for exercise prescription in patients with bone metastases: A comprehensive narrative review. *PM R* 2018;10(8):843-864. doi:10.1016/j.pmrj.2018.02.006.

9. Wang A, Obertová Z, Brown C, et al. Risk of fracture in men with prostate cancer on androgen deprivation therapy: a population-based cohort study in New Zealand. *BMC Cancer* 2015;15:837. doi:10.1186/s12885-015-1843-3.

10. Alibhai SMH, Duong-Hua M, Cheung AM, et al. Fracture types and risk factors in men with prostate cancer on androgen deprivation therapy: a matched cohort study of 19,079 men. *J Urol* 2010;184(3):918-923. doi:10.1016/j.juro.2010.04.068.

11. Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005;352(2):154-164. doi:10.1056/NEJMoa041943.

12. Townsend MF, Sanders WH, Northway RO, Graham SD. Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. *Cancer* 1997;79(3):545-550. doi:10.1002/(SICI)1097-0142(19970201)79:3<545::AID-CNCR17>3.0.CO;2-3.

13. Klaassen Z, Howard LE, de Hoedt A, et al. Factors predicting skeletal-related events in patients with bone metastatic castration-resistant prostate cancer. *Cancer* 2017;123(9):1528-1535. doi:10.1002/cncr.30505.