IMAJ • VOL 13 • FEBRUARY 2011

Meta-Analysis of Unexpected Findings in Routine Histopathology during Total Joint Replacement

Guy Rubin MD[1], Semion Krasnyansky MD[1], Israel Gavish MD[2], Irit Elmalah MD[3], Oren Ben-Lulu MD[1] and Nimrod Rozen MD PhD[1,4]

[1]Department of Orthopedics, [2]Hematology Unit and [3]Department of Pathology, HaEmek Medical Center, Afula, Israel
[4]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Routine histopathological analysis of bone extracted during total joint replacement is controversial.
Objectives: To evaluate the utility of routine histopathological analysis in total joint replacement.
Methods: We calculated the risk for discrepant diagnosis between the pre- and postoperative histopathological results by performing a meta-analysis of 11 studies (including our data). We also calculated the risk for significant discrepancies.
Results: The discrepant diagnoses analysis showed a random effect of 3% discrepancies (95% confidence interval 1.2–3.7%). Funnel plot indicates a publication bias; consequently, the conclusions from this analysis should be interpreted with caution. Regarding the significant discrepancy in diagnosis, we performed a meta-analysis of nine studies. Fixed-effects analysis of all the studies resulted in 0.16% significant discrepancies (95% CI 0.02–0.30%) with no heterogeneity ($Q = 3.93$, degrees of freedom = 9, $P = 0.14$, $I^2 = 49.2\%$), and appropriate fixed-effects models.
Conclusions: We recommend no further routine histological examination, reserving this tool for cases with a controversial primary diagnosis and unexpected findings during the operation.

IMAJ 2011; 13: 80–83

KEY WORDS: oint arthroplasty, occult malignancy, meta-analysis, unexpected diagnosis

Joint arthroplasty is a very common procedure. During this procedure bones are removed and replaced with an implant. Bones can either be sent to a bone bank for routine pathological examination to confirm preoperative diagnosis, or destroyed. When bones are sent to a bone bank they must be examined according to recommendations of the Musculo-Skeletal Council of the American Association of Tissue Banks [1] or the European Association of Musculo-Skeletal Transplantation [2]. These recommendations do not include histopathology examination. Pathological examination can ensure safety for the recipient by eliminating the transmission of a malignancy [3].

CI = confidence interval

In order to confirm the preoperative clinical diagnosis many surgeons send the removed bone for pathological examination. This option is debatable due to cost and effectiveness; however, the results sometimes reveal unexpected findings with different clinical significance. In order to assess the risk for discrepancy between pre- and postoperative histopathological diagnoses we performed a meta-analysis of bones sent for histopathologic examinations following joint replacement in addition to those described in the literature. The clinical significant discrepancy percentage was calculated.

MATERIALS AND METHODS

IDENTIFICATION AND SELECTION OF STUDIES

We performed a literature search using the MEDLINE computerized database for articles published from 1966 to 2008. Our purpose was to identify all the pertinent publications including the key words: joint, hip, knee, arthroplasty, joint replacement, unexpected diagnosis, and unexpected malignancy. We also performed a search of our patients' files and the bibliographies of all the included articles. We discovered 10 pertinent abstracts or full-text articles during our literature search, which we reviewed and included in our meta-analysis. Studies were selected for inclusion on the basis of strict methodological criteria: a) the patients had to have been treated with elective primary total joint arthroplasty, b) only studies that described results of routine histopathological examinations were selected, c) case reports were excluded, and d) a consecutive series of 67 femoral heads retrieved during elective total hip arthroplasty in our department were included.

ANALYSIS

The log odds of a discrepancy were calculated and logistic regression was performed since many of the studies had a small number of discrepancies. Wherever there were 0 discrepancies 0.5 was added in order to calculate the odds. To accommodate for the pooling of multiple trials, the 95% confidence interval for each risk was calculated using a logistic regression model. With this approach, the width of the estimated confidence interval is increased as compared to the standard approach, ignoring the correlation between observations within a study [4,5].

Table 1. Discrepant diagnoses in 11 studies

Study	No. of cases	No. of discrepancies	% of discrepant diagnoses	Odds	Log odds
Sugihara et al., 1999 [6]	137	5	3.65%	0.038	-3.273
Kocher et al., 2000 [7]	1234	28	2.27%	0.023	-3.763
Raab et al., 1998 [8]	168	16	9.52%	0.105	-2.251
Lawrence et al., 1999 [9]	1388	0	0.00%	0.000	-7.236
Campbell et al., 1997 [10]	715	6	0.84%	0.008	-4.772
Meding et al., 2000 [11]	951	27	2.84%	0.029	-3.533
Pagnano et al., 1998 [12]	2289	10	0.44%	0.004	-5.429
Di Carlo, 1992 [13]	1794	97	5.41%	0.057	-2.862
Fornasier and Battglia, 2005 [14]	460	3	0.65%	0.007	-5.027
Palmer et al., 1999 [15]	1146	91	7.94%	0.086	-2.450
Rubin et al. (present study)	67	5	7.46%	0.075	-2.584
Fixed effects				0.048	-3.03
Random effects				0.024	-3.72

RESULTS

OUR DATA

A total of 67 consecutive cases were included in this study. Of the 67 patients we found 5 incidental diagnoses that did not concur with the primary diagnosis (6.9%). Of the five cases, there were three low-grade, B cell, non-Hodgkin's lymphoma, one enchondroma and one avascular necrosis. The lymphoma pathology specimens showed focal infiltration with nodules of small B lymphocytes. Immunohistochemical staining was positive for CD20. A thorough hematological evaluation was performed in patients including image staging with isotope imaging positron emission tomography-FDG, which was negative. Abdominal ultrasonography demonstrated normal spleen and liver amplitude. Lactate dehydrogenase and beta-2-microglobulin were in the normal range. The patients were asymptomatic and it was concluded that non-Hodgkin's lymphoma was an incidental finding.

DISCREPANT DIAGNOSES

We identified ten studies that met the entry criteria [6-15]. From a total of 10,349 patients (including our study) there were 287 discrepancies (2.7%). The percentage of discrepant diagnoses ranged from 0.0 to 9.5 [Table 1]. In all but one of these studies the percentage of discrepancies was significantly different from 0. Fixed-effects analysis of all the studies revealed a value of 1.12% discrepancies (95% confidence interval 0.9–1.3%). Random-effects analysis demonstrated a value of 3.0% discrepancies (95% CI 1.7–4.4%). Figure 1 shows the Forest plot of the data. The Forest plot reveals few non-overlapping intervals, indicating a possible lack of heterogeneity. Formal tests for heterogeneity indicate the presence of high heterogeneity (Q=178.4, degrees of freedom = 10, $P < 0.01$, $I^2 = 94\%$), suggesting that fixed-effects models should not be used. The Funnel plot shows asymmetry (a linear decreasing trend), which is an indication of publication bias [Figure 2]; therefore, conclusions from this analysis need to be interpreted with caution.

SIGNIFICANT DISCREPANCIES

As shown in Table 2, 10 of the 11 studies showed significant discrepancies, 9 of which resulted in a change in treatment. Fixed-effects analysis of all the studies showed 0.16% signifi-

Figure 1. Forest plot of the 11 studies, with squares representing the percent discrepancies, and lines the 95% confidence interval

Study	Exposed AM[e]SE[e]	Control AM[c]SE[c]	Weight (%)	Association measure with 95% CI
Sugihara et al., 1999 [6]	-3.27/0.43	-3.27/0.43	2%	-3.27(-4.11 to -2.44)
Kocher et al., 2000 [7]	-3.76/0.19	-3.76/0.19	10%	-3.76 (4.13 to -3.4)
Raab et al., 1998 [8]	-2.25/0.25	-2.25/0.25	6%	-2.25(-2.73 to -1.77)
Lawrence et al., 1999 [9]	-7.24/1	-7.24/1	0%	-7.24(-9.2 to -5.28)
Campbell et al., 1997 [10]	-4.77/0.39	-4.77/0.39	2%	-4.77(-5.54 to -4)
Meding et al., 2000 [11]	-3.53/0.19	-3.53/0.19	9%	-3.53(-3.91 to -3.16)
Pagnano et al., 1998 [12]	-5.43/0.31	-5.43/0.31	4%	-5.43(-6.03 to -4.82)
Di Carlo, 1992 [13]	-2.86/0.1	-2.86/0.1	33%	-2.86(-3.06 to -2.66)
Fornasier and Battglia, 2005 [14]	-5.03/0.54	-5.03/0.54	1%	-5.03(-6.07 to -3.98)
Palmer et al., 1999 [15]	-2.45/0.11	-2.45/0.11	31%	-2.45(-2.66 to -2.24)
Rubin et al. (present study)	-2.58/0.47	-2.58/0.47	2%	-2.58(-3.51 to -1.66)
Meta-Analysis			100%	-3.03(-3.14 to -2.91)

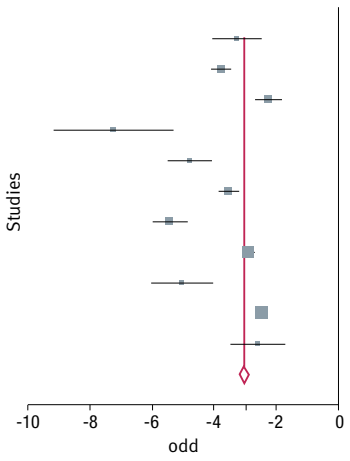

Figure 2. Funnel plot of the 11 studies

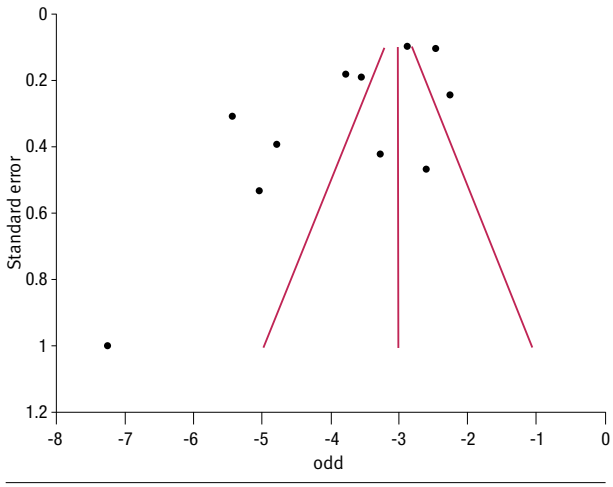

Table 2. Significant discrepant diagnoses in 10 studies

Study	No. of cases	No. of significant discrepancies	% of diagnoses*	Odds	Log odds
Sugihara et al., 1999 [6]	137	0	0.00%	0.0004	-4.92
Kocher et al., 2000 [7]	1234	1	0.08%	0.0008	-6.713
Raab et al., 1998 [8]	168	1	0.60%	0.0060	-4.718
Lawrence et al., 1999 [9]	1388	0	0.00%	0.0000	-7.236
Campbell et al., 1997 [10]	715	0	0.00%	0.0001	-6.572
Meding et al., 2000 [11]	951	0	0.00%	0.0000	-6.858
Pagnano et al., 1998 [12]	2289	0	0.00%	0.0000	-7.736
Di Carlo et al., 1992 [13]	1794	7	0.39%	0.0039	-5.477
Fornasier et al., 2005 [14]	460	0	0.00%	0.0001	-6.131
Rubin et al. 2011	67	0	0.00%	0.0009	-4.043
Fixed effects				0.0030	-5.81
Random effects				0.0026	-5.96

cant discrepancies (95% CI 0.02–0.30). A Forest plot of the data [Figure 3] indicates homogeneity among the studies. No heterogeneity was found in a heterogeneity test (Q = 15.29, degrees of freedom = 9, $P = 0.08$, $I^2 = 41\%$) and fixed-effects models are appropriate. Random-effects analysis revealed a value of 0.04% (95% CI -0.07–0.15) for significant discrepancies in all studies. The Funnel plot indicates no publication bias [Figure 4].

DISCUSSION

Based on the literature review, histopathological examination of bone removed during total joint replacement is controversial for two reasons: the cost-effectiveness of this procedure when performed routinely, and the recipient's safety when examination is not performed prior to arrival at the bone bank. We found ten articles that compared the pre- and postoperative diagnoses. From among the 10,349 patients (including those in our study) who participated in these studies, 287 discrepancies (2.7%) were found. Significant discrepancies that resulted in a change in the patients' treatment include one case with osteomyelitis (Raab et al. [8]) and seven cases described by DiCarlo et al. [13] who did not report the clinical outcome. In addition, Sugihara and co-researchers [6] found four cases of asymptomatic non-Hodgkin's lymphoma and claimed that since the possibility of disease transmission is not clear, pathological examination is justified. Palmer et al. [15] found 91 discrepancies but did not describe their clinical significance.

The meta-analysis showed values of 3.0% (95% CI 1.7–4.4%) for random effects of discrepant diagnoses and 0.16% for fixed effects of significant discrepancies (95% CI 0.02–0.30%). This meta-analysis reinforces most of the authors' conclusions, namely, not to perform routine histopathology examinations [7,9-12].

In accordance with the literature, we recommend reserving the tool of histological examination exclusively for cases with a controversial primary diagnosis, unexpected findings during surgery, and/or cases where the femoral head will be used as an allograft even though the possibility of malignancy transmission is not yet determined.

Acknowledgment

We thank Paula Herer for the statistical analysis, and Tova Bick, Frances Nachmani and Georget Nemirovsky for their help preparing this manuscript for publication.

Corresponding author:
Dr. G. Rubin
Dept. of Orthopedics, HaEmek Medical Center, Afula 18101, Israel
Phone: (972-4) 649-4300
email: guy_ru@clalit.org.il

References

1. Standards for tissue banking. American Association of Tissue Banks, 1996.
2. Common standards for musculoskeletal tissue banking. European Association for Musculoskeletal Transplanting, 1997.
3. Tomford WW. Current concepts review: transmission of disease through transplantation of musculoskeletal allografts. *J Bone Joint Surg* 1995; 77A:1742-54.
4. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KGM. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. BMC Medical Research Methodology 2006, 6(50). http://www.ncbi.nlm.nih.gov/pubmed/17038197?dopt=Citation
5. Bax L, Yu LM, Ikeda N, Tsuruta N, Moons KGM. MIX. Comprehensive free software for meta-analysis of causal research data, version 1.7. http://www.mix-for-meta-analysis.info; 2008.
6. Sugihara S, van Ginkel AD, Jiya TU, van Royen BJ, van Diest PJ, Wuisman PI. Histopathology of retrieved allografts of the femoral head. *J Bone Joint Surg* 1999; 81-B(2): 336-41.
7. Kocher MS, Erens G, Thornhill TS, Ready JE. Cost and effectiveness of routine pathological examination of operative specimens obtained during primary total hip and knee replacement in patients with osteoarthritis. *J Bone Joint Surg* 2000; 82-A(11): 1531-5.
8. Raab SS, Slagel DD, Robinson RA. The utility of histological examination of

tissue removed during elective joint replacement: a preliminary assessment. *J Bone Joint Surg* 1998; 80-A: 331-5.

9. Lawrence T, Moskal JT, Diduch DR. Analysis of routine histological evaluation of tissues removed during primary hip and knee arthroplasty. *J Bone Joint Surg* 1999; 81-A: 926-31.
10. Campbell ML, Gregory AM, Meuerhan DR. Collection of surgical specimens in total joint arthroplasty. Is routine pathology cost effective? *J Arthroplaplasty* 1997; 12(1): 60-3.
11. Meding JB, Ritter MA, Jones NL, Kearting EM, Faris PM. Determining the necessity for routine pathologic examinations in uncomplicated total hip and total knee arthroplasties. *J Arthroplasty* 2000; 15(1): 69-71.
12. Pagnano MW, Forero FH, Scuderi GR, Harwin SF. Is the routine examination of surgical specimens worthwhile in primary total knee arthroplasty? *Clin Orthop Relat Res* 1998; (356): 79-84.
13. DiCarlo EF. Pathology of the femoral head. *Mod Pathol* 1992; l7: 10.
14. Fornasier VL, Battaglia DM. Finding the unexpected: pathological examination of surgically resected femoral heads. *Skeletal Radiol* 2005; 34(6): 321-8. Epub 2005 Feb 17.
15. Palmer SH, Gibbons CL, Athanasou NA. The pathology of bone allograft. *J Bone Joint Surg* 1999; 81-B(2): 333-5.