Estimate of the risk of cancer caused by radiation therapy of Dupuytren's Disease

Introduction

This estimate has been carefully prepared but its accuracy cannot be guaranteed. **The International Dupuytren Society e.V. explicitly waives any liability for its application or for related damages. Estimating a statistical risk cannot make any predictions for individual cases.**

Section 1 describes the earlier estimate prepared by the International Dupuytren Society in cooperation with GSF for the risk of skin cancer. Section 2 describes results of more recent publications, and section 4 describes other side effects of the radiation therapy (radiotherapy) of Dupuytren's Disease.

1. Estimating the risk of skin cancer

Assumptions

1. A single hand is radiated with a total dose of 30 Gy. This is the dose typically used for x-ray therapy of Morbus Dupuytren or Ledderhose. If both hands are irradiated, then the dose and risk of cancer are doubled.
2. The radiated area is assumed as 60 cm² (which is fairly large, typically irradiated areas are smaller) . The remaining hand and body are sufficiently protected during treatment.
3. Usually the treatment is fractioned, e.g. into 5 x 3 Gy (e.g. 3 Gy each on five consequent days) + 5 x 3 Gy (the radiation application is repeated after a 4 - 6 weeks break). This break gives the radiated skin time to recover and reduces the immediate radiation damage. The fractioning is ignored in below estimate because it does not affect the risk of cancer.
4. Radiation therapy of Morbus Dupuytren typically uses low energy x-rays (50 - 150 kV Bremsstrahlung). It is likely that this relatively low energy reduces the risk of cancer but this is ignored below because no scaling factors are available.
5. The chances of developing lethal cancer depend on age. For a young patient of 25 years the chance of developing cancer is probably twice as high as for someone 45 years old (45 years = about factor 1). The risk sinks with increasing age, e.g. at the age of 60 the age factor is about 0.5. This effect is ignored in the estimate below.
6. Research indicates that patients with Dupuytren's might have a higher risk of dying from cancer (see e.g. Gudmundsson KG; Arngrímsson R; Sigfússon N; Jónsson T, Increased total mortality and cancer mortality in men with Dupuytren's disease: a 15-year follow-up study, Journal of clinical epidemiology 1 (2002) p 5 - 10). It is unclear whether and to what extent this affects the risk of cancer due to radiation therapy but we assume that is doubles the risk. The actual effect is probably smaller, if it exists at all.
7. To calculate the risk only the skin is taken into account. Other irradiated parts of the hand are ignored because there the risk is far less (but we are still trying to assess the risk for sarcoma).
8. No additional risk factors exist. In the case of skin cancer one could, for example, consider additional strong sun exposure but the palm of the hand (Morbus Dupuytren) and the arch of the foot (Morbus Ledderhose) typically have very little exposure to the sun.
9. The calculation assumes a standard person. Individual deviations in size and weight are probably irrelevant but could easily be taken into account by anyone interested.

Estimate

Every skin cell has received a dose of 30 Gy. It is not necessary to additionally scale the energy or involved mass. The dose definitions used here are according to e.g. German DIN 6814-3 of 2001.

Because the skin is an extended organ the energy dose when radiating a part a part of it has to be averaged over the whole skin area to calculate an Effective Dose. The total skin area is assumed to 2 m² = 20.000 cm². We further assume that the radiation fully penetrated the hand, i.e. that the front and back of the hand were equally exposed. Neglecting absorption 120 cm² of skin were thus exposed with 30 Gy.

This results in an *Organ Energy Dose* of the skin of
(120cm² x 30 Gy + (20000 cm² - 120 cm²) x 0 Gy)/20000cm² = 0.18 Gy
Using the radiation weight factor of x-rays (=1 Sv/Gy) we calculate the organ dose of the skin to be 0.18 Sv = 180 mSv.
Effective Dose E = sum over all exposed organs x respective tissue weight factor wT.
As we consider skin only we get
E = organ dose of skin x 0.01 = 1.8 mSv
The risk coefficient to develop lethal cancer is currently estimated in literature as 0.005% per mSv. According to the possibly higher risk of Dupuytren's patients [5] we are doubling this factor to 0.01% per mSv.
This results in a risk coefficient of

1.8 mSv x 0.01%/mSv = 0.018% = approx. 0.02%

This risk may be compared with the **natural lethal cancer coefficient** of **23.945% +/- 0.261%**. The probability of dying from cancer without radiation therapy is about 24 % (+/- 0.26%). With radiation therapy this value increases by about 0.02%. This increase would be impossible to actually observe and measure because the calculated increase is significantly less than the degree of uncertainty of the natural lethal cancer coefficient.

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2. Extended estimate

A recent paper by Jansen et al. [4] not only takes into account skin cancer but also various organs, muscles, bones, and bone marrow (red). Though the paper does not explicitly estimate the effect of radiotherapy of Morbus Dupuytren, the results for heel spurs are applicable for Ledderhose and Dupuytren's disease as well, within the limits of accuracy.
For a male patient of 50 years the effective dose due to radiotherapy of a heel spur (using 200 kV x-rays, dose 12 Gy, area 80 cm²) is estimated for skin cancer purposes to be 2.9 mSv, similar to our above estimate. Taking into account other contributions the effective dose is estimated to 8 - 9.5 mSv.
The paper calculates the increases risk for acquiring cancer due to radiotherapy of heel spurs (based on phantom calculations of Adam/male and Eve/female; cf. table 5 of the above cited paper):

Age at time of radiotherapy:	25 years	50 years	75 years
Adam model (men):	0.1 percent	0.04 percent	0.01 percent
Eva model (women):	0.2 percent	0.05 percent	0.02 percent

The risk of cancer calculated in this paper is higher than our original estimate for skin cancer alone (by a factor of about 4 because radiation of Dupuytren usually applies to a smaller area though it often uses about double the dose). In total the add-on risk is still very small compared to the natural risk and the authors conclude "For effective doses below 10 mSv, which is about four times the annual background radiation burden (2.8 mSv per year), the benefit of a probable cure or prevention of a disease will compensate the risk easily." We would like to mention that Seegenschmiedt et al. estimate "the theoretical risk for induction of soft tissue sarcoma or skin cancer to 0.5-1 % after latency periods of 8-30 years" [6]. The authors don't refer to age at this estimate, only mentioning "children and younger adults", therefore their results might be difficult to compare with our estimate.

It should also be kept in mind that so far not a single case of cancer due to radiation therapy of Dupuytren's Disease has been documented. - For younger patients the risk of cancer is higher. The factor of 2 between men and woman (at 25 and 75 years of age) is probably not real but due to rounding, the actual difference being smaller (more like that shown at 50 years).

3. Please comment!

The International Dupuytren Society wants to inform as objectively and correctly as possible. If you find any errors in this estimate, if you have any critique, or would like to comment on it, please email w.wachx=xdupuytren-online.de, replacing x=x with the usual @ sign in e-mail addresses. Thank you for your contribution!

4. Other side effects of radiation therapy

While the above estimate indicates that the additional risk of acquiring cancer due to radiation therapy is very low, radiation therapy can also have other immediate and undesired side effects. The related probabilities are typically much higher. For example Adamietz et al. report in a long term observation of 176 radiated hands that about 25% of the hands exhibited anhidrosis (dryness), 8.5% skin athropy (reduced nutrition of the skin) and below 1% reduced wound healing. For Ledderhose patients Seegenschmiedt and Attassi observed dryness at 8% of the radiated 36 feet. Other side effects might also be possible and are e.g. described on our web site www.dupuytren-online.info .

5. Literature on radiation therapy

[1] Adamietz B, Keilholz L, Grunert J, Sauer R. "Radiotherapy of early stage Dupuytren disease. Long-term results after a median follow-up period of 10 years" Strahlenther Onkol 177 (2001) p 604 - 610. - In German. English abstract.

[2] Seegenschmiedt MH, Olschewski T, Guntrum F "Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study" Int. J. Radiat. Oncol. Biol. Phys. 49/3 (2001) p 785 - 798.

[3] Keilholz, L, Seegenschmiedt MH, Sauer R "Radiotherapy for prevention of disease progression in early-stage Dupuytren's contracture: initial and long-term results" Int. J. Radiat. Oncol. Biol. Phys. 36 (1996) p 891 - 897.

[4] J. Jansen, J. Broerse, J. Zoetelief, C. Klein, and H. Seegenschmiedt "Estimation of the carcinogenic risk of radiotherapy of benign diseases from shoulder to heel" Radiotherapy and Oncology 76 (2005) p 270 - 277.

[5]Gudmundsson KG, Arngrímsson R, Sigfússon N, Jónsson T. "Increased total mortality and cancer mortality in men with Dupuytren's disease: a 15-year follow-up study" J Clin Epidemiol 55 (2002) p 5-10.
[6] H. Seegenschmiedt et al "Long-term outcome of Radiotherapy for Early Stage Dupuytren's Disease: A Phase III Clinical Study" in Ch. Eaton et al. (Eds.) "Dupuytren's Disease and Related Hyperproliferative Disorders" (Springer, Heidelberg & New York, 2012), p 349-371, here specifically p 364.

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