POSITIVE TRENDS IN RADIATION RISK ASSESSMENT AND CONSEQUENT OPPORTUNITIES FOR LINAC APPLICATIONS

Y. Socol, Falcon Analytics, Hanevel Str. 13/1 Karney Shomron, 4485500 Israel

Abstract

Ionizing radiation, an unavoidable by-product of high-energy LINACs, makes them subject to strict regulation and severe public concerns. During the last two decades the attitude to ionizing radiation hazards has been becoming more balanced, as opposed to the historical "radiophobia". The linear no-threshold hypothesis (LNTH), based on the assumption that every radiation dose increment constitutes increased cancer risk for humans, is more and more debated. In particular, the recent memorandum of the International Commission on Radiological Protection (ICRP) admits that the LNTH predictions at low doses (that ICRP itself has used and continues to use) are "speculative, unproven, undetectable and "phantom'." Moreover, numerous experimental, ecological, and epidemiological studies show that low doses of ionizing radiation may be beneficial to human health. While these advances in scientific understanding have not yet given fruit regarding radiation regulation and policy, we are hopeful these may happen in near to middle term. The presentation reviews the present status of the low-dose radiation-hazard debate. It also outlines anticipated opportunities for wider LINAC applications, especially in the prospective field of low-dose radiation therapy.

CONTROVERSY OVER THE LINEAR NO-THRESHOLD HYPOTHESIS

The linear no-threshold (LNT) hypothesis (LNTH) of radiation-induced cancers implies that every dose of ionizing radiation, no matter how small, constitutes increased (linear with the dose) cancer risk. This hypothesis, which became well-established for use in radiation safety during the Cold War era increasing fears of nuclear apocalypses in background, is presently used for low-dose radiation cancer risk assessment by advisory bodies, and as such it is the basis for current radiation safety regulations. The LNTH is also widely accepted by the general public. However, the scientific validity of this hypothesis has been questioned and debated for many decades without resolution. The disagreement on this issue in the scientific community has always been acknowledged by relevant professional bodies, including the US Congress Office of Technology Assessment [1].

Two recent examples below demonstrate how mistreatments of experimental data continue to lend support to the LNTH.

A-bomb Survivors

The results of the atomic bomb survivors follow-up are often claimed to support the LNTH [2]. However, this claim is baseless. The cancer mortality of the survivors is equally or better described by an s-shaped dependence on radiation exposure [3] with a threshold of about 0.3 Sievert (Sv) and saturation level at about 1.5 Sv (Fig. 1, left). Moreover, Monte-Carlo simulation of possible outcomes demonstrates that, given the weak statistical power, the follow-up cannot provide support for LNTH. The data that were generated according to s-shaped (a priori) distribution (with variance $Var = 1$), could be well-described (a posteriori) by a straight line (average $Var \approx 1.5$), as shown at Fig. 1, right. E.g., if we use fit variance $Var > 2.0$ as a cut value to exclude LNTH, we have to reject the correct s-shaped description in about 0.5% of cases (7 out of 1000 in this simulation); still we have to accept LNTH in nearly 90% of cases (877 out of 1000 in this simulation).

CT Scans and Childhood Cancer

CT scans are of high clinical usefulness as a valuable diagnostic technique, and new applications continue to be identified. However, the increasing use of CT scans is being challenged by emerging concerns regarding carcinogenesis from the ionizing radiation. Pearce et al. [4] made a significant contribution to the above concerns by claiming, probably for the first time, evidence for direct association of the radiation from CT scans with cancer. However, data points on cancer relative risk vs. CT-dose in their publication fit LNTH straight lines suspiciously-well, taking into account relatively large statistical errors (Fig. 2). The chi-square goodness-of-fit test demonstrates quantitatively that the data are likely "too good to be true". For leukaemia, there are six dose groups (squares in Fig 2, left). The first data group is used for risk normalization, and there is one parameter – LNT slope s. The number of degrees of freedom is 4=5–1, corresponding to 5 independent dose groups and 1 parameter. For brain tumours (eight dose groups), the number of degrees of freedom is 6=8–2. The expected (average) values $\langle\chi^2\rangle$ are therefore 4.0 and 6.0 for leukaemia and for brain tumors, while the actual fitted χ^2 values are 1.19 and 2.91 correspondingly. The corresponding p-values are 0.12 and 0.18. Here the p-value is the probability that χ^2 will be equal or less than the obtained value, i.e. that the fit will be that good or better. Since the two data sets are expected to be independent, the resulting probability of both fits being that good or better simultaneously is $0.12\times0.18 \approx 0.02$. This is below the generally-assumed threshold of $p_{thr} = 0.05$, so the data are statistically *inconsistent* with the LNTH. The credibility of the data is therefore compromised. Most probably, some kind of data manipulation was performed, possibly unknowingly, by the authors of [4].

ISBN 978-3-95450-142-7

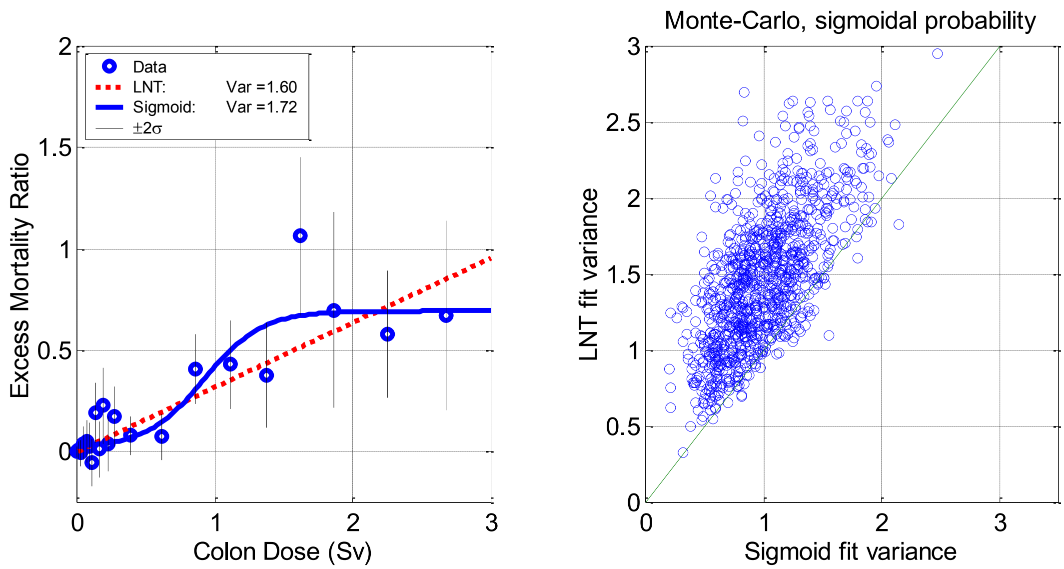

Figure 1: The cancer mortality of the survivors can be described by an s-shaped dependence on radiation exposure with a threshold of about 0.3 Sievert (Sv) and saturation level at about 1.5 Sv; such description is not worse than the linear one (left). Moreover, Monte-Carlo simulation of possible outcomes demonstrates that, given the weak statistical power, the follow-up cannot provide support for LNTH (right). Source: Socol and Dobrzyński [3].

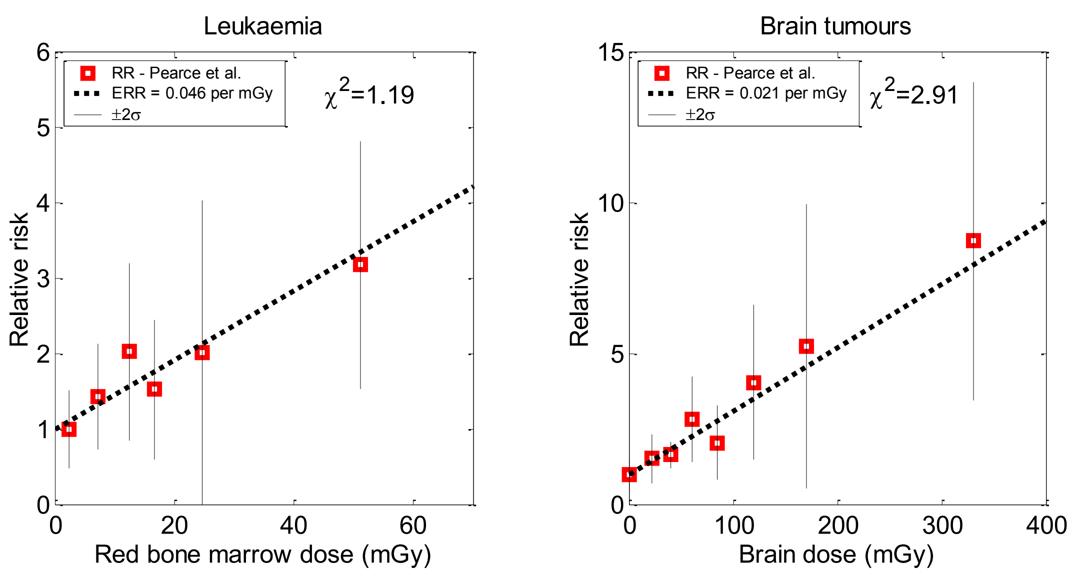

Figure 2: The data points on cancer relative risk vs. CT-dose reported by Pearce et al. [4] fit LNTH straight lines suspiciously-well, taking into account relatively large statistical errors. By applying rigorous statistical analysis, one can see that the probability of both fits to be that good or better simultaneously, is 2% only. The credibility of the data is therefore compromised. Most probably, some kind of data manipulation was performed, possibly unknowingly, by the authors of [4].

Beneficial Health Effects of Low Doses

Furthermore, there is phenomenon called "hormesis" which is a consequence of adaptive response: while large amounts of some factor are detrimental, small doses are beneficial. Classical examples of hormesis are physical exercise (as opposed to extreme forced labour) and immunization (as opposed to infection). Low doses of biologically-active ultraviolet radiation are also hormetic – limited sun tanning (as opposed to sunburns and skin cancer caused by overexposure). Numerous experimental and epidemiological studies show that low doses of ionizing radiation are probably hormetic. E.g., in most of the nuclear industry workers studies, the rate of cancer mortality (as well as overall mortality) among the radiation workers is substantially lower than in the reference population – see e.g. the US shipyard workers study [5,6]. Radon treatment is definitely not considered

ISBN 978-3-95450-142-7

to be an "alternative therapy" by the mainstream medicine in Europe, especially for treating arthritis and other inflammatory diseases. Superiority of radon therapy as compared to a control intervention in rheumatic out-patients, has been recently reported [7]. Actually, the healing properties of radon spas have been utilized for many centuries – as described by Herodotus and Hippocrates for springs with high concentration of radon in their water, as we know now. The above facts and many others [8,9] comprise emerging scientific support for the radiation hormesis hypothesis.

Low-dose whole-body irradiation for cancer treatment (as opposed to high-dose tumour irradiation, or radiation surgery) has been studied decades ago in USA [10] and more recently, mainly in Japan [11]. In the study of Sakamoto et al. [12], 84% of leukaemia patients who underwent low-dose irradiation supplementary treatment, survived 9 years. In the control group, the 9-year survival ratio was 50% only (Fig. 3).

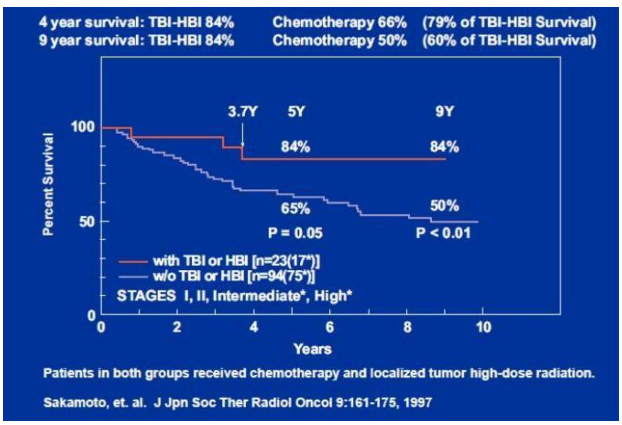

Figure 3: Survival ratio of leukaemia patients – with and without low-dose total body irradiation (TBI) or half-body irradiation (HBI) treatment. Out of TBI- or HBI-treated, 84% survived 9 years. In the control group, the 9-year survival ratio was 50% only [12].

POSITIVE TRENDS (EVENTS SINCE LINAC12)

While the use of LNTH is still a commonplace, there are at least three positive signs with reference to its eventual overthrow. These are: (a) offensive on LNTH and defensive stance of LNTH supporters, (b) softening of the advisory bodies' position on LNTH, and (c) pro-nuclear changes in Japan.

Offensive on Linear No-Threshold hypothesis

In 2013, a new international professional action group was formed: Scientists for Accurate Radiation Information [12]. After its first year of existence, the group numbers about 80 members – health professionals, physicists, educators, writers. SARI has created an easy-to-use web site (http://RadiationEffects.org) stocked with useful reference documents. The group wrote open letters to officials and official bodies (including the Prime Minister of Japan), professional societies and radiation health effects advisory groups. The SARI members have published journal articles and provided coordinated comments.

Two recent publications should be specially mentioned since they show a new trend. Namely, these are disputes where the LNTH supporters take defensive positions instead of just ignoring the anti-LNTH evidence, which was a standard practice in the past. In one case [13,14], Ralph Cicerone, the NAS President, defends his position against Edward Calabrese – the chairman of the International Dose-Response Society. In the second case [15], Mark Little – co-author of the above-discussed paper claiming association of cancer with CT scans – defends his position against Mohan Doss – one of the active SARI members.

Softening of the Advisory Bodies' Position on LNTH

The recent memorandum of the ICRP (International Commission on Radiological Protection) Task Group [16] contains the following statement:

"*While prudent for radiological protection, the LNT model is not universally accepted as biological truth...*

Speculative, unproven, undetectable and 'phantom' *numbers are obtained by multiplying the nominal risk coefficients by an estimate of the collective dose received by a huge number of individuals theoretically incurring very tiny doses that are hypothesised from radioactive substances released into the environment*." (highlighted by YS).

So the Task Group of the ICRP, one of the main bodies promoting the LNT model, admits that LNT predictions at low doses are "speculative, unproven, undetectable and 'phantom'," raising the reasonable wonder how such a model can be "prudent for radiological protection." The position of ICRP towards LNTH is not new, but has never been formulated earlier in such unambiguous expressions.

Another example is the position of the International Atomic Energy Agency (IAEA). In its recent document [17] IAEA stated that in case of nuclear power plant accident, radiation level below 2.5 mrem/hour (about 100-times natural background) is "safe for everyone." This statement, though made with several comments, should be viewed as big progress in respect to the usual position "there is no safe level of radiation". And just an additional example, UNSCEAR in its 2013 report to the UN Assembly [18] predicted "no discernible health effects" of the Fukushima nuclear accident.

Japan: Pro-nuclear Changes

After the Fukushima accident in March 2011, about 160,000 residents of the Fukushima prefecture have been evacuated and all the nuclear power plants in Japan were stopped due to the radiation concerns. During 2013-2014, however, the attitude to the radiation hazards began to change. One can mention at least three important developments. Already in mid-2012, the government began partial resettlement of the Fukushima prefecture

[19], and this trend persists till now. In Feb 2014, Yōichi Masuzoe, known for his pro-nuclear views, was elected governor of Tokyo. In April, the Japanese cabinet approved the new energy strategy, effectively scrapping the after-Fukushima plans for nuclear power phase-out [20].

APPLICATIONS

Probably all present and prospective applications of LINACs should benefit from the improved radiation risk assessment.

Medical

As discussed above, use of low-dose radiation in treatment (and prophylaxis) of cancer is extremely interesting [11]. It seems that low-dose irradiation may substitute chemotherapy for some types of cancer, especially for non-localized like leukaemia or angiosarcoma (cancer of blood or lymphatic vessels). However, such research is presently in a very preliminary stage.

On the other hand, anti-inflammatory action of low-dose ionizing radiation is well known. As mentioned above, anti-arthritic action of radon springs has been utilized for centuries. Moreover, during the first half of the twentieth century, ionizing radiation was very successfully utilized for the treatment of many inflammatory and infectious conditions. E.g., an estimated 500,000 to 2 million individuals, mostly children, were treated with Nasopharyngeal Radium Irradiation in the US only [21] for inner ear infections and related conditions. No adverse long-term effects were observed [22]. Two simultaneous trends slowed and ultimately stopped all non-cancer use of irradiation: development of effective antibiotics, and emerging concerns regarding carcinogenesis from low-dose radiation. Presently, there are concerns about development of antibiotic-resistant disease germs [23, 24]. With declining efficiency of the antibiotic treatment, irradiation (low-dose but high-energy) may prove to be a vital and viable alternative.

FELs for Semiconductor Lithography

The idea to use extreme ultraviolet free-electron laser (EUV FEL) for semiconductor lithography at 13.5 nm is not new [25,26]. However, it seems that during the last year this idea has been seriously considered by the industry [27]. The radiation issue does not seem to be the main obstacle in EUV FEL development – the main obstacle is the necessity to perform extensive R&D. Nevertheless, it is plausible to expect that easing of the radiation regulations and changing of the public perception of radiation hazards will positively affect the ability of FELs to compete other light sources.

Miscellaneous

Electron LINACs may be used for food sterilization, leading to the reduction in supply-chain losses and to extended shelf life. Since the irradiated food does not become radioactive, the main obstacle to the spread of this technology seems to be related to the public misunderstanding of radiation hazards. With more realistic attitude to radiation hazards, the market for LINAC-irradiated food is anticipated to grow considerably.

Irradiation leads to intensification of important chemical processes, such as polymerization or curing in composites. In high-volume production, the radiation doses for the workers are relatively high unless expensive shielding is installed. Since the plastics industry is generally regarded as low-tech with relatively cheap labour, upgrading the employees officially to a status of "radiation workers" does not seem to be a viable option in the present situation. However, the situation will change dramatically with easing of the radiation regulations and changing of the public perception of radiation hazards.

All other LINAC applications, including sterilization of medical materials and utensils, gem colouring etc., will also benefit from easing the radiation regulation and elimination of radiophobia.

CONCLUSIONS

During the last two decades the attitude to ionizing radiation hazards has been becoming more balanced, as opposed to the historical "radiophobia". The linear no-threshold hypothesis (LNTH), based on the assumption that every radiation dose increment constitutes increased cancer risk for humans, is more and more debated. Particularly, the recent memorandum of the International Commission on Radiological Protection admits that the LNTH predictions at low doses are "speculative, unproven, undetectable and "phantom'." Moreover, numerous experimental, ecological, and epidemiological studies show that low doses of ionizing radiation may be beneficial to human health.

Therefore, use of LINACs for low-dose radiation in treatment (and prophylaxis) of cancer, first studied four decades ago, is extremely interesting. It seems that low-dose irradiation may substitute chemotherapy for some types of cancer, especially for non-localized like leukaemia or angiosarcoma (cancer of blood or lymphatic vessels). Another important field of medical applications is related to anti-inflammatory action of low-dose ionizing radiation: anti-arthritic action of radon springs has been utilized for centuries. Moreover, during the 1-st half of the 20-th century, ionizing radiation was very successfully utilized for treatment of many inflammatory and infectious conditions, including treatment of inner ear infections in children. With declining efficiency of the antibiotic treatment, irradiation (low-dose but high-energy) may prove to be a vital and viable alternative.

Other applications, including potential 13.5-nm FEL for semiconductor lithography, are also anticipated to gain from balanced risk assessment, regulation and public opinion regarding radiation.

ISBN 978-3-95450-142-7

ACKNOWLEDGMENTS

The author wishes to thank all the colleagues from SARI (Scientists for Accurate Radiation Information) who participated in the discussions and provided material. Special thanks to Prof. Ludwik Dobrzyński (National Centre for Nuclear Research, Poland) and to Prof. Mohan Doss (Fox Chase Cancer Center, US).

REFERENCES

[1] Office of Technology Assessment, Congress of the United States, *The Effects of Nuclear War*, (London: Croom Helm, 1980), 111.

[2] K .Ozasa et al., “Studies of the Mortality of Atomic Bomb Survivors, Report 14, 1950–2003: An Overview of Cancer and Noncancer Diseases”, Radiation Research 177(3), 229–243 (2012).

[3] Y. Socol, L. Dobrzhynski, “Atomic Bomb Survivors Life-Span Study: Insufficient Statistical Power to Select Radiation Carcinogenesis Model”, Dose-Response, in print.

[4] M.S. Pearce M.S, Salotti JA, M.P. Little et al., “Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study”, Lancet 380, 499–505 (2012).

[5] R. Sponsler, J.R. Cameron, “Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation”, Int. J. of Low Radiation 1, 463–478 (2005).

[6] G. Matanoski “Health effects of low-level radiation in shipyard workers. Final report”. Report No. DOE DE-AC02-79 EV1005. US Department of Energy, Washington, DC, USA (1991).

[7] A. Franke, T. Franke, “Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial”, Rheumatol Int 33, 2839–2850 (2013).

[8] E.J. Calabrese. “Hormetic Mechanisms”, Critical Reviews in Toxicology 43, 580–606 (2013).

[9] L.E. Feinendegen, M. Pollycove, R.D. Neumann, “Hormesis by Low Dose Radiation Effects: Low-Dose Cancer Risk Modeling Must Recognize Up-Regulation of Protection”, In: R.P. Baum (Ed.) *Therapeutic Nuclear Medicine*, (Springer, 2013).

[10] J.T. Chaffey et al. “Total body irradiation as treatment for lymphosarcoma”, Int J Radiat Oncol Biol Phys, 1, 399–405 (1976).

[11] K. Sakamoto. “Radiobiological Basis for Cancer Therapy by Total or Half-Body Irradiation”, Dose-Response 2, 293–316 (2004).

[12] K. Sakamoto et al., “Fundamental and clinical studies on cancer control with total or half body irradiation”, J Jpn Soc Ther Radiol. 9, 161–175 (1997).

[13] E.J. Calabrese, “How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response”, Arch Toxicol. 87, 2063–81 (2013).

[14] R.J. Cicerone RJ, K.D. Crowley, “Letter from Ralph J Cicerone regarding Edward Calabrese's paper published online first on August 4th: "how the US national academy of sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response".” Arch Toxicol. 88, 171–2 (2014).

[15] M. Doss, M.P. Little, C.G. Orton. “Point /Counter-point: Low-dose radiation is beneficial, not harmful”, Med. Phys. 41, 070601 (2014).

[16] A.J. Gonzalez et al., “Radiological protection issues arising during and after the Fukushima nuclear reactor accident”, J. Radiol. Prot. 33, 497–571 (2013).

[17] *Placing the Radiological Health Hazard in Perspective in an Emergency due to Severe Conditions at a Light Water Reactor* (Vienna: IAEA, 2013), http://www-ns.iaea.org/downloads/iec/health-hazard-perspec-charts2013.pdf

[18] United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) *Sources and effects of ionizing radiation. UNSCEAR 2013 Report to the General Assembly, with Scientific Annexes*. (NY: United Nations, 2013).

[19] World Nuclear News website: “Early returns to Fukushima”, http://www.world-nuclear-news.org/RS_Early_returns_to_Fukushima_0204121.html (02 April 2012).

[20] World Nuclear News website: “Japan retains nuclear in energy mix”, http://www.world-nuclear-news.org/NP-Japan-retains-nuclear-in-energy-mix-1104147.html (11 April 2014).

[21] Centers for Disease Control and Prevention website: “Nasopharyngeal Radium Irradiation (NRI)”, http://www.cdc.gov/nceh/radiation/brochure/profile_nri.htm

[22] E.J. Calabrese and G. Dhawan, “Historical use of x-rays: Treatment of inner ear infections and prevention of deafness”, Human and Experimental Toxicology 33, 542–553 (2014).

[23] M.L. Cohen, “Changing patterns of infectious disease”, Nature 406, 762–767 (2000).

[24] R.F. Khabbaz et al., “Challenges of infectious diseases in the USA”, Lancet 384, 53–63 (2014).

[25] C. Pagani et al., “Design considerations of 10 kW-scale, extreme ultraviolet SASE FEL for lithography”, Nucl. Instrum. Methods Phys. Res., Sect. A 475, 391–396 (2001).

[26] Y. Socolet al., “Compact 13.5-nm free-electron laser for extreme ultraviolet lithography”, Phys. Rev. ST Accel. Beams 14, 040702 (2011).

[27] T. Uchiyama. “Current status and expectation of EUV lithography”, 2014 International Workshop on EUV Lithography, Maui, Hawaii, June 23-27, 2014. http://www.euvlitho.com/2014/P3.pdf