Once upon a time in oncology - will we definitely win a war against cancer? Critical review of the progresses in cancer therapies

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Once upon a time in oncology – will we definitely win a war against cancer? Critical review of the progresses in cancer therapies

Bogusław Maciejewski, Daniel Bula, Justyna Rembak-Szynkiewicz

Aim of the present review of various classic and novel therapeutic strategies in oncology is critical discussion of its efficacy to answer whether once upon a time is it real and possible to win a war against cancer. Although technological progress in radiotherapy (RT) has led to develop many sophisticated 3D, 4D techniques, the use of the RT as a sole modality has become more and more limited to the tumours in early stage of disease, in favour of combined surgery-RT-chemotherapy (CHT) therapies. Nevertheless patients curability has never reached the level higher than 95% (stereotactic hypofractionated RT – limited too small tumours only). The CHT for solid malignant tumours is not effective enough, and therefore it is mainly combined with Surg and RT as a method of the boost. Common use of partial or complete regression (PR, CR) as end-points of its efficacy is irrelevant, since it is quasi-quantified tumour cell clearance but not cell kill effects, and the regrowth delay (time of tumour regrowth to the size, volume at the beginning of therapy) is the only proper end-point. Efficacy of various genetic, molecular, immuno, and antiangiogenic modalities tested in many clinical studies is critically discussed, and it has generally showed some therapeutic benefits, but not very spectacular. It has been well documented that genotypes and phenotypes of the tumours (even within the same location, stage and histology) are individually highly heterogeneous. Therefore, the term “average probability” referred to individual patients becomes meaningless, and moreover, this term has never been replaced by “certainty” yet. Statistics of many studies and trials consist of various pitfalls and biases.
Thus, although we and our patients are more often winners on the individual battlefields, the winning once upon a time of whole war against cancer seems to be possible (hope), but not for sure (real).

**Key words:** malignant solid tumours, efficacy of various therapeutic modalities, probability vs. certainty, statistical pitfalls and biases

The first though, which crosses one’s mind, trying to answer to the title question might be “never say never”, but “once upon a time” would sound more promising. Enormous number of studies in many fields of oncology, genetics, molecular biology and tumour immunology have gathered a large clouds of results and comments, which look promising, but not necessarily encouraging a lot. Therefore, to work out a dilemma, whether one can win or not, needs to consider and discuss the results and achievements of various classic, recent and novel therapeutic modalities used or tested in the realm of oncology.

**Innovations in radiotherapy - physics and not only**

Technological progress in radiotherapy has brought to the market a wide sort of high-tech accelerators emitting high energy photons, electrons, protons and particle beams, which have been used to develop a precise 3,4 D-conformal IMRT, IGRT, IART techniques. Sophisticated algorithms optimizing dose distribution to maximize therapeutic differences between tumour and normal tissue responses came to daily practice, based on an interplay of physics, biology and clinical oncology [1–11]. It may look as a pronounced promise of a new era in radiotherapy. But it does not always happen, although the RT offers wide range of treatment time and dose intensity. Expectations of the outcome improvement are immutably based on an a simple assumption (or even belief) that the tumour appeared on the CT/MRI images is limited to their bounds, what is not often true at all.

The RT seems an attractive offer, because it often claims a success, but it remains unclear to what that “success” refers – to permanent curability or to local tumour control only. Withers [10], Le [11] and Glatstein [17] have warned that 3-D conformal RT techniques result in a heterogeneous dose distribution, which hides discrepancy between physical and
biological doses, and the risk of “overconformality”. Some tumours with an indolent proliferation activity, such as prostate cancer, chordomas, meningiomas, acoustic neuromas, and some normal tissues as well, are highly sensitive to change in the dose per fraction, expressed by a low $\alpha/\beta$ ratio. For a long time, we have been convinced fans of the $\alpha/\beta$ concept. However, with the time passing, some uncertainty has been growing and growing up, and suggested that tumour and surrounding normal tissues consist of various cellular structures, as blood vessels and its epithelium, hypoxic cellular microlesions, muscles, nerves, etc., which respective $\alpha/\beta$ values differ, and therefore, an average $\alpha/\beta$ may also differ as well. Therefore, it is unknown, whether alpha or beta or may be even gamma value is correct [18], what can tangle up in misleading conclusions and results. In fact, the $\alpha/\beta$ formalism is rather incidentally used in the daily RT planning.

A great leap forward in the RT equipment and techniques it is not supported by a long-term local cure benefits, which has occurred lower than expected. In the past, the results of a large number of the trials on altered fractionation became rather disappointing lesson, with an average 6% tumour control benefit [12–15]. Patients with generally poor prognosis are candidates to studies on a new RT strategies. The question is whether objective evaluation of 3-D IMRT, IGRT, IART efficacy has ever been done or not [18, 19]. There are obviously no convincing results regarding lung cancer [16–19], and some other advanced cancers, irrespectively of any theoretical rationale for potential benefits.

Patients expected to live long (e.g., breast or pediatric cancers, etc.) may manifest some of unforeseen morbidities that have not yet been precisely reported. Before the start of therapy, prediction of the events in the past, (tumour control, late side effect) is based on the gathered incidences of such events, but it has never been judged whether specific event will occur for sure, or not. There is true inconsistency between tumour control probability (TCP) expected before the treatment, and local tumour control (LTC), what is noted as the result of therapy. The TCP or the risk of complication (NTCP) is the frequency of the event which may occur, and it is considered as a numerical mapping of the degree to which we believe the event will occur. Therefore, “Is this a game of chance?” – “No, it is the way we play it” (W.C. Fields in 36).

Radio-biological principles are rather rarely accounted for the RT planning. Assumption the TCP, of let say 99% (TCP = $e^{-0.01}$), suggests that 10 of 1000 patients, or 100 of
10,000 patients will fail, that means the RT local curability is not universal. In the case of the SHRT, the LTC of 85–95% can be achieved using single dose or a few high fractions, but for small tumours only. On the other hand, using the 3D-IMRT, IGRT, IART techniques, even small “cold spot” within the PTV (overconformality), often missed during evaluation of the DVHs, leads to significant decrease in the TCP, and therefore, in the LTC as well. The Heraclits’ sentence “you can’t step in the same river twice” – means for the RT, that the same tumour should not be irradiated twice, and reirradiation is used seldom and rarely satisfactorily effective. Simple reason is that the planned reirradiation dose is inexplicably but commonly lower (40–50 Gy) than curative one, although regrowing tumour cells proliferate much, much faster than native cancer cells, and therefore recurrent tumour logically needs higher radical dose than primarily delivered.

The RT and surgery as local therapeutic modalities are directed to where the tumour exists, and the theoretical aim is a complete elimination of clonogenic cancer cells, proliferating unlimitedly, what can theoretically lead to the patient’s cure. However, it remains unknown whether and how many microcolonies of cancer cells are beyond surgical or irradiated margins, and where they really are. Clinical situations, which RT or surgery is used in alone, have significantly been reduced, and replaced by pre- or post-operative radiotherapy, and/or chemotherapy. Such combinations of two or three modalities have been found successful for head and neck cancer, but not necessarily for the lung or rectal cancers [20–23].

Till the middle 80-ties, various treatment modalities offered for locally advanced cancers were palliative options mainly. Then, reconstructive surgery initiated in the US in the 1980-ties, later in the West European countries, and around 2000 in Poland, has made a breakthrough in the treatment of these tumours, mainly H&N, sarcomas and childhood solid malignancies. But that method is limited to individually selected patients. Although an overall therapeutic benefit increased, but not very much.

The major failure of many tumours is almost the same – distant metastases, which can subclinically be present even at the time of treatment or likely for some time before [21, 24]. It remains unknown, how effective is numerical eradication of clonogenic cancer cells being below the level of its clinical detection. If a few cancer cells survive, they will be the source of local recurrence for sure, and in the case of cell mutations, also the source of
metastatic lesions. In case of the ovarian cancer, distant metastases are the major cause of failure, since the cancer cells spread over whole abdominal cavity, and they grow intensively and reveal clinically as advanced disease. Thus, surgery is usually limited to palliative cytoreduction, followed by chemotherapy. There is no room for the RT, although in the 60-ties some attempts were made, using “moving strips” technique. However, that method was abandoned, because the strips overlapped and resulted in serious acute intestinal and bone marrow complications.

Among long list of malignancies, glioblastoma multiforme is the unique one. Although surgery and/or RT, with or without temodal, are used with radical intent, neither long-term LTC nor DFS have ever been achieved and reported, and the OS is also very short. The enigma of this malignancy is that even if the gross tumour mass disappears as the result of local therapy, malignant glioma cells already circulate in the brain blood vessels network, controlled by the feedback regulatory system of the hypoxic and angiogenetic processes, which mutually activate each other.

Distant metastases are not the only attribute of the advanced tumours. Even in the case of early stage of the cancer (e.g. breast cancer), distant metastases (DM) may occur early within the first 18 months of follow-up, with the rate of 8–23%, as it was reported by Kryj et al [26], what suggests that the distant metastases can already be present at the time of surgery. Thomlinson [25] rightly pointed out, that the breast cancer should be considered as a systemic disease, and the cytotoxic chemotherapy should be the modality used at the beginning of therapy. Therefore, it should not surprise, that in contrast to high-tech innovations, the use of the RT as a sole treatment has been more and more limited in favour of combined therapies which sequences are individually tailored, and defined as theragnostic oncology.

**Power of chemotherapy – sequential or concurrent**

Chemotherapy (CHT) acts within and out of the tumour bounds. In general, the candidates to that form of therapy are advanced tumours with a pronounced risk of dissemination. When cytotoxic agents are injected intravenously, there is however, no further control and a low knowledge about their destination. Therefore, principal cause of the CHT failure is
inadequate delivery of the drug to some part of tumours because of the poor local blood
flow, which in clinical situations can sometimes only be deduced, but not measured. But this
is not the only reason.

Thomlinson [24, 25] designed and carried out a milestone study, which included
62,000 measurements of tumour volumes made in 239 breast cancer patients, treated with
RT or CHT, and produced 748 tumour regression curves. The Achilles' heel of the CHT is that
multiagent cycles are spaced out by 1–3 weeks, to overcome epithelial and lymphopenia side
effects, and to limit its severity to the level of patient' tolerance. Making frequent measures
of tumour size (volume) of the breast cancers, Thomlinson [24] noted that tumour partly
regresses directly after each cycle of the CHT, and regrows later in a cyclic manner during
sparing breaks between cycles (fig. 1C). This universal pattern was termed as "Jeffs
phenomenon". It clearly shows that, although intensity of the acute side effects decreases
during breaks between the CHT cycles, tumour clonogenic cells don't sleep and wait, but
repopulate pretty fast, resulting in the tumour regrowth. Therefore the resultant average
tumour regression curve is much shallower than that noted directly after each one cycle.
After surgery or RT, tumour deceleration is much deeper (fig. 1A and B), than after CHT, but
the final number of the survived tumour cells also remain unknown. When an average
number of the survived tumour cells would be equal 0.001, then the LTC will raise to 99.9%
(unrealistic). It means that 10 of 10,000 patients may fail after the treatment, and in fact
100% cancer curability can never be predicted, and achieved, since the cell survival rate is
the result of a random cell killing, and decreases asymptotically with no chance to reach zero.

Tumour gets smaller (regression) during and after therapy, only when dead
clonogenic cells are removed out of the tumour. Thomlinson [24, 25] clearly documented
that regression rate of the same tumour type varies individually, and its spectrum is about
50-fold wide after identical and constant dose of the RT or CHT (fig. 2). There are three
formal, clinical end-points to quantify the CHT efficacy in the clinic, i.e. Minimal Response
(who knows what does it quantitatively mean?), partial regression and complete regression
(fig. 1C). This is astounding, that for more than 5 decades, the PR and CR have been
persistently used in practice, despite the fact that they are clinically irrelevant and it makes
no adds, since they mark the removal of already dead cells by various heterolytic processes
only, resulting in the decrease of tumour doublings from about 35–36 (e.g. 3.5–4 cm tumour
diameter) to 29–30 (0.5 cm³ tumour), which is still a too short way to the local tumour control. Therefore, the PR and CR with no doubts, do not quantify the CHT cell kill effect. Long time ago, it was clearly pointed out that the only proper quantitative of end-point the CHT effect is the regrowth delay (RD), which measures time period, during which recurrent tumour regrows to the size (volume) at the start of the CHT (fig. 3). In the case of long-term LTC, the RD achieved infinity.

The CHT used as a sole modality to treat solid malignant tumours is not radical, curative therapy, except leukaemias and some lymphomas. Therefore, it has often been used as neo- or adjuvant tools. However, metaanalysis of the CHT combined with RT [27] revealed only an average 2% therapeutic benefit after neo- or adjuvant CHT (result seems to be within the range of statistical error). Concurrent chemo-radiation produces a bit higher LTC gain of about 6% [28]. Such, an average benefit looks suspectedly too low. Therefore, to check that results we reviewed well documented 15 selected studies on concurrent RT-CHT (cisplatin, 5-Fu or paclitaxel) carried-out in the world-leading cancer centers (3300 H&N cancers). The 3-year LTC has been higher by about 20% [11–26%] than the RT alone. So, previous metaanalysis results recommended as an “evidence” guide seems at least doubtful. Large number of studies suggest that surgery (fig. 1A) and radiotherapy (fig. 1B) have possible but not certain curative power (100% LTC has never been achieved), but not the CHT (fig. 1C). So, we can win some individual battles with cancer, but not yet a whole war.

**Genetic and molecular tumour biology and therapeutics perspectives – belief on, or not**

During the last 3–4 decades, enormous amount of data have been gathered regarding genomics, proteomics, radiomics and tumour biology [29–31]. Growing recognition of the heterogeneity of genotypes and phenotypes of tumour cells, tumour supresor genes and intra-cellular multisignaling pathways has led to initiation of many attempts to develop and to test in practice various specific antibodies, which could modify and enhance therapeutic power of classic treatment modalities. One of the interesting approach is targeting the signaling axes of cancer stem cells (CSC) alone or in combination with CHT and/or RT. It has been proved that survival of even one CSC leads to recurrence for sure. Actually, the combination of CHT with CSC inhibitor GDC-0449hais been tested for the advanced, primary
or recurrent small cell lung cancer. In case of melanoma, the use of immune check-point inhibitors targeting cytotoxic T-lymphocyte-associated protein CTL4 has occurred clinically promising. Preclinical studies on TGF-β1-neutralizing antibodies have offered interesting strategy to prevent radiation induced fibrosis. Some experimental studies have shown that the VEGFR-2 blocking antibody may decrease the dose of fractionated radiotherapy. By contrast to a fear of destruction of tumour vasculature by antiangiogenic therapy, some studies have shown the normalization of tumour vasculature in various pilot clinical studies on HER-2-negative breast cancer, NSCLC, rectal, hepatocellular, ovary cancers and glioblastoma multiforme. Regarding the last malignancy the concept has developed that the block of more than one cellular receptor could be more efficient, and pilot the US study on anti-VEGFR2 together with anti-EGFR were combined with the RT. The results were highly disappointing, with no therapeutic benefit, but with high, over 50% rate of brain lethal necrosis. It may likely suggest, that the use of more than one antibody is too much to be tolerated by patients.

Many studies focused on antiangiogenic therapy (fig. 4), have finally showed surprisingly short and disappointing extension of the progression-free survival, by only 1.2–6 months, and also very low improvement in overall survival (by 1.4–4.7 months), achieved only for the selected patients [29], although many pilot and randomized studies documented the feasibility and reliability of molecular modifiers combined with CHT-RT for different malignant tumours [30–34]. Similarly, quests of validity molecular predictors [34] have shown that some of them correlate with higher LTC or even DFS. But, it has to be pointed out, that interpretation of correlation’s power may differ, and the correlation coefficient of $r = 1.0$ only, defines strong and absolute “predictor-effect” relationship, whereas in many relevant studies, the factor $r$, even it is higher than 0.5, has never reached 1.0. So far, clinical power of the family of tested genetic and molecular predictors can only be interpreted in the category of “likelihood”, but not as absolute and undoubtful guideline. Numerous clinical studies, which extensively explore growing knowledge on genomics and proteomics of human malignant tumours to test novel concepts of combined therapeutic strategies, are very important and should not be ignored, but the progress in the patients’ curability can only be achieved by small steps by steps forward, and for complete victory of the war against cancer we still have to wait.
Interesting aim of some experimental and clinical studies is to intensify processes of the host immune response against primary and metastatic cancer cells by immunotherapy combined with the RT and/or CHT. It has been found out that immunogenicity is mediated by the DNA exonuclease Trex1, which could be used as a potential biomodulator to optimize the RT combined with the CHT. Complimentary pathway is TGF-β, which promotes the RT to induce antitumour immunity. Actual results convince the stereotactic hypofractionated RT (SHRT) should be considered a potentially highly effective treatment, since the use of a large single dose or a few large fractions effectively boosts by tumour immune-response (fig. 5), triggering in situ vaccination, T-cell promising infiltration, and immunogenetic killing [30, 32]. Large doses of RT induce Fas-receptors, which activate the T-cells. Pre- and clinical studies have shown a complexity of the processes optimizing radiation-immunotherapy interactions. The SHRT frequently used in the setting of limited extra- and intracranial metastases combined with immunotherapy could provide not only the LTC improvement, but also distant control as well. Immune agents approved for cancer therapy include cytokines, oncolytic viruses, dendritic-cell vaccine and check-point inhibitors. There is well-grounded excitement to design studies exploring RT combined with available immunotherapeutic strategies.

Another fast-growing field in the oncologic therapies is a combination of diagnostic and therapeutic modalities with nanoparticles [30]. The use of Nano-Radiation Dose Enhancer (Nano-RDE) to improve RT efficacy has been one of the explored fields by experimental and pilot clinical studies, and has been termed as a “SMART combined modality therapy” [30]. Gold nano-particles (Au NP) have been tested to intensify both the CHT and the RT efficacy. The TNFα – colloidal gold nanoparticle (CYT-6091) selectively delivered to the cancer cells intensifies apoptotic effect of the RT dose. However, till now, such compounds are not used in the routine daily RT practice yet. Nevertheless, interesting approach concerns the use of direct conjugation of antibody labeled with radionuclide, compatible with SPECT or PET imaging, to localize antibodies in the tumour, inducing cytoreductive and potentially curative effect (targeted drugs). Major obstacle is, however, insufficient dose delivery to solid tumours because of a poor penetration. With no doubts, all these new approaches are very interesting and encouraging, but they are still at the beginning of “a long, long way to Tipperary”. As it happened before, some of them will likely
be abandoned, and others will be extensively explored. But, they still remain within probabilityland, and not in an absolute certaintyland of the victory.

**Miracle of statistics – pitfalls and biases?**

One may raise a query about statistical interpretations of the clinical data [18, 19]. Roots of statistics of the “cause-effect” relationships are in the 19th century laws of physics and mathematics, which are immutable. If something occurs, then that must follow. However, it does not happen in the oncology at all. There is a large individual genetic, phenotypic, biological variables and pathways, which make a large number of more or less powerful variables of “cause-effect” relationships very difficult to be explicitly establish. Discussing the results of various brilliant concepts and attempts made to win a war against cancer, major question arises to why the results of major therapeutic achievements are much lower than expected. It seems that one important reason is that randomization and stratification routinely explored in the trials, produce only ostensibly homogenous groups of patients, whereas in fact, they are genetically, fenotypically and biologically highly individual tumours, and therefore highly heterogeneous, even if its localization, type and stage are the same. Since the result of such wide spread of heterogeneities are usually quantified as “averages” or “median”, one can generally be disappointed with rather low therapeutic gain reported. The averages are usually recognized as significant when the “p” value is below 0.05. But according to Glatstein [18, 19], significance does not necessarily mean clinical importance. If, for example p-value is 0.06, the results are counted as insignificant. However, are the results really less clinically important when 94 instead of 95 of 100 patients with cancer will be permanently cured? Somebody could say – “not at all statistically”, since it they differ by one patient only. But clinically – cure of the one is as important as a cure of the other 100 patients, and the p-value is just a statistical toy to play with the analyzed results of treatment.

Interpretations of the “averages” usually lead to uncertainties and doubts. It is a routine procedure to comment survival (LTC, DFS, OS) curves couting actuarial vs crude survival. The first one often leads to underestimations, since the cases lost during 3-, 5-, 10-years follow-up are censored in about 50% as relapses, whereas they might be controlled...
during the assumed follow-up. Another point of criticism is that the interpretation of the survival curves simplifies their courses to the one number, which is a median value. It seems that the major problem is that the interpretation are focused on one point on the survival curve and its trail is usually ignored. Meanwhile, such curve is surrounded by the “noise” of many points, representing individual patients. If, for example in some trial, 5-year actuarial LTC of the H&N cancer would be about 85% in the tested arm and 70% in the conventional one, then such difference will be quantified for sure as statistically significant, in favour of a novel therapy. But, what is often ignored is that, for example in the control arm 15% rate of local recurrences have occurred during the first 18 months of the follow-up [26]. It becomes clearly evident, based on biology, and kinetics of tumour growth, that such small subclinical tumour cell lesions beyond the irradiated or operated area likely already exist at the time of the start the therapy. Therefore, it should not be accounted for the efficacy of the conventional therapy. When such part of the LTC curve would be excluded, than both curve become close each other and significance disappears, and the advantage of the tested therapy as well. This is an example of the statistical bias, which often happens.

Important trouble with interpretation of the trials and metaanalyses results is that the actuarial statistics reflect wide biological and genetic heterogeneities of patients and maldistribution of various prognostic factors, although, at the first glance, they look homogenous within each study group. For head and neck cancers, about 600 genetic and proteomic predictors were analyzed couple years ago and none of them turned out to be absolute and the sole prognostic predictor. However, when Buffa et al. [34], have analyzed that sets of data once again using sophisticated taxonomic cluster statistics, they have clearly found overexpression of the four factors as a significant prognostic predictors of the LTC gain by 20%. Similarly, Suwiński et al. [35] designed the trial, to test efficacy of the 7 fractions per week vs conventional 5 fractions per week, used in the postoperative radiotherapy for H&N cancer patients with the increased risk of local recurrences. Classic, actuarial statistics have shown no difference in the effectiveness of both schedules. But, when the authors designed molecular scoring for the overexpression of the four selected genetic predictors, then the score >2 of them predicted enormous increase in the DFS after 7 fractions/week schedule, much, much higher (>40%) than after 5 fractions/week. In case of the score ≤2 there is in favour of any these two schedules. These examples, and also many others as well, suggest
that classic statistic provide deceptive results. Therefore, a rhetorical question may arise
what should be considered as “evidence”. It seems that in many studies importance of the
“evidence” remains uncertain. Thus, clinicians should likely prefer clinical importance,
experience, and common sense as a guidelines, more than the results predominately based
on the p-value. Glatstein [18, 19] strongly suggests that the “evidence” should be weighed
more carefully, and it seems that in case of individual patients, the logic and own experience
are often more important, but it does not mean that the trials should be dismissed.

Conclusions

Many years ago, famous oncologist Vincent de Vita pointed out that “if we expect
pronounced success in oncology, we have to be patient, because the progress will be realized
in many small steps”. For the last few decades, our knowledge on genetics, proteomics
molecular predictors and modifies has enormously increased, and we have unexpectedly
learned that there are as many genetically and phenotypically different malignant diseases as
many patients suffer from them. It means, that effective combined therapy should be
personally individualized, and we are not able to win a total war against cancer yet. But, we
should not lose the hope and belief that it can happen on the future. There is a large number
of winners on various, single oncologic battlefields, mainly those, which tumours are in very
early stage of disease. Undoubtedly, we will likely achieve important step forward when we
will be able to replace “probabilityland” by “certaintyland”, but not yet. We should also keep
reasonable and limited belief on the statistics, and remember that the “averages” never
represent individual heterogeneous characteristics. So far, real progress in the cancer
curability can likely be expected due to the increased activity and efficacy of the prophylaxis
and early detection of malignant tumours.

Article information and declarations

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Boguslaw Maciejewski – 75%
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Figure 1. Theoretical tumour cell survival curves after: A – surgery; B – radiotherapy; C – chemotherapy. MR-minimal response; PR-partial regression; CR-complete regression; x-average number of survived cells. CHT curves-reprinted from Thomlinson [24]
Figure 2. Spectrum of regression rate of the breast cancers after delivery the same and constant dose of the RT or CHT, estimated by Thomlinson [24, 25]

Figure 3. Scheme illustrating how to measure “regrowth delay” as the only quantitative
end-point of the CHT efficacy. Extrapolation of the tumour regrowth curves (dotted red lines) back to cell survival coordinate allows to estimate approximate decrease in the cell kill effect of a given CHT

Figure 4. Improvement in progression –PFS and OS after antiangiogenic therapy (taken from Jain et al. review [29])

Figure 5. Scheme of immunostimulation of the indirect cancer cell death induced by
high doses of the SHRT [32]. DAMPs – set of molecular factors which induce indirect immunological lethal effect