Review Article

Why we should give spatially fractionated radiation therapy (GRID) a second look—especially in nasopharyngeal carcinoma

Sharon S. Poh[1], Melvin L. K. Chua[1,2], Joseph T. S. Wee[1,2]

[1]Division of Radiation Oncology, National Cancer Centre Singapore, 169610 Singapore, Singapore; [2]Duke-NUS Medical School, 169857 Singapore, Singapore

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Correspondence to: Joseph T. S. Wee, FRCR. Duke-NUS Medical School, 169857 Singapore, Singapore; Division of Radiation Oncology, National Cancer Centre Singapore, 11 Hospital Drive, 169610 Singapore, Singapore. Email: joseph.wee.t.s@singhealth.com.sg.

Abstract: GRID or spatially fractionated radiation therapy was historically used in the orthovoltage era to deliver large single 15–20 Gy doses of radiotherapy to tumours greater than 6 cm by creating a dosimetric distribution that is comprised of intervening "hot" and "cold" spots within the tumour. However, despite impressive response rates of 70% with GRID at such non-tumoricidal doses, the technique quickly fell out of favour with the advent of megavoltage linear accelerators. With the introduction of modern techniques like stereotactic body radiation therapy (SBRT) that have produced comparable response rates, it is possible that a commonality between both modalities pertains to the influence on the adaptive immune response within the tumour microenvironment. Here, we review the clinical evidence and potential mechanisms underpinning the clinical efficacy of GRID; we also propose potential scenarios where GRID represents a cost-effective and safe measure of delivering profound hypo-fractionated radiation therapy in the contemporary setting.

Keywords: Nasopharyngeal carcinoma (NPC); spatially fractionated radiation therapy (GRID); spatially fractionated radiotherapy; radiosurgery; ablative body radiotherapy; immune modulation; abscopal; checkpoint inhibitors; chemo-immunotherapy

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Introduction

Radiation therapy (RT) using the spatially fractionated radiation therapy (GRID) technique has had a very long history, since the early 20th century. GRID RT is performed by the administration of high-dose radiation through a perforated block of radio-dense material, rather than open fields, thus effectively spatially fractionating the beam into several pencil beamlets, with sparing of the skin and tissues in between. This allowed large doses to be delivered in a single fraction, which was particularly relevant in the early days of RT, where the only machines available were those delivering ortho-voltage. Without a technique to modulate the skin dose, ortho-voltage machines deposited their maximum dose at the skin surface, thus limiting doses that could be used due to skin toxicity. Using the GRID technique allowed the areas of skin and subcutaneous tissue that were spared to act as centres of regeneration, allowing higher doses to be used, with much reduced toxicity.

Since then, with the advent of megavoltage linear accelerators (LINACs) gaining widespread use in RT, with its skin sparing properties, the primary purpose for the use of GRID was negated, and this treatment technique has largely fallen out of favour.

However, interest remains in the use of GRID in combination with palliative RT using megavoltage machines, especially in palliative cases, where excellent response has been achieved (1-3). The benefit of this

Table 1 Summary table—response to GRID therapy

Symptom	Complete response (CR) (%)	Partial response (PR) (%)	Overall response (OR) (%)
Palliative—pain	19.5	58.5	78.0
Palliative—mass effect	14.6	52.9	72.5
Palliative—bleeding	50.0	50.0	100.0

technique is 2-fold:

(I) Allowing high doses to be delivered (in a single fraction or a few weekly fractions over several weeks), without the absolute need for CT scans and complex treatment planning procedures. This is especially advantageous in developing countries where easy access to healthcare may be difficult, as well as countries with large disease burdens, where waiting time for treatment may be long. This also allows for dose escalation, which would usually not be feasible with conventionally fractionated radiation alone. Conventional external beam RT (EBRT) can still be used after GRID to deliver further dose to the tumour;

(II) Possible effects of spatially fractionated radiation on immune modulation. High doses of radiation to tumour cells may result in the production of substantial cytokines that have a bystander effect in killing adjacent non-irradiated or partially irradiated cells under the closed areas of the grid, thus further improving tumour cell kill beyond that expected from just radiation alone (1).

As a result, the use of GRID can be envisioned in two forms; as a way of delivering palliative RT, especially in cases where the tumour is bulky and symptomatic, as well as in a form of "neoadjuvant" treatment for harnessing the immune-activating properties of GRID treatment before the delivery of definitive radical treatment.

Published clinical effectiveness of GRID

There have been a number of published studies looking at the effectiveness of GRID therapy, both in palliative cases, administered in a single fraction; as well as in combination with definitive chemo-RT in radical treatment.

Palliative

In a study by Mohiuddin *et al.* evaluating the effectiveness of GRID therapy in the treatment of advanced and bulky cancers, it was observed that GRID therapy resulted in good response with minimal toxicity (1). A total of 63 patients received palliative treatment in this study, with the abdomen and pelvis as the predominantly treated sites, followed by head and neck, thorax, and extremities. GRID RT was administered using a megavoltage beam of 6 MV photons delivered through a 50:50 GRID (open to closed area) with single doses ranging from 10 to 20 Gy. Good response was observed in the relief of pain [78.0% overall response (OR); 19.5% complete response (CR)], mass effect (72.5% OR; 14.6% CR), bleeding (100.0% OR; 50.0% CR) and dyspnoea [60.0% partial response (PR)] (*Table 1*); squamous cell carcinoma and adenocarcinoma were the histological subtypes that had the best responses. Among acute side effects, there was a case of mortality due to rapid tumour lysis and carotid blowout, as well as a grade 3 mucositis with eventual recovery. No grade 3 and above late skin, subcutaneous, mucosal, gastrointestinal or central nervous system complications were observed.

Radical treatment

Penagaricano *et al.* reported on their results using GRID RT with chemotherapy followed by conventional intensity modulated RT (IMRT) in the radical treatment of large bulky locally advanced head and neck squamous cell carcinoma (4). They studied a total of 14 patients all with tumours larger than 6 cm, who were all given a single fraction of 20 Gy delivered by GRID RT before the start of RT. Chemotherapy was administered with GRID (various protocols: mainly carboplatin-docetaxel), and continued on as per usual concurrent chemo-RT protocol with the start of conventional IMRT to 66 Gy to the planning target volume in 30 fractions, which started the next day after GRID. Results showed pathologic and clinical CR rates of 79% (11 of 14) after planned neck dissection or primary tumour biopsies in the GRID field, which is superior to the reported response rates in published series for patients with combined N2 and N3 disease (65%) or N3 alone (54%) receiving radical chemo-RT without GRID (5-7). Toxicity

and complication rates with GRID RT and without GRID RT appear to be similar, with the most common acute skin and mucosal toxicities being grade 3 and 2, respectively.

Mohiuddin *et al.* also carried out a small study in 17 head and neck cancer patients with large bulky tumours greater than 8 cm in size (1). Single fraction GRID therapy of 10–20 Gy was given as part of a definitive treatment combined with conventionally fractionated external beam irradiation (dose range of 50–70 Gy), followed by subsequent surgery. Clinical CR was observed in 62.5% of patients and a pathological CR was confirmed in the operative specimen in 50% of the patients after GRID and conventional EBRT. Traditionally, using only conventional techniques, such large tumours would usually have responded poorly to radiation, and would have been unlikely to have been considered surgically operable.

These studies serve to illustrate that GRID therapy is able to offer good local control of disease, both for palliation and radical treatment in a selected population, especially where conventional treatment alone has a limited chance of success due to large tumour size leading to unfavourable radiobiology using conventional RT dose fractionation. Furthermore, GRID RT can be safely combined with full-dose conventionally-fractionated RT to achieve significant dose escalation, improving local control without any significant worse acute or late toxicity or compromising subsequent surgery or wound healing.

Potential role of GRID in nasopharyngeal carcinoma (NPC)

NPC is endemic in many low-to-middle-income countries/regions. As a result of poor access to healthcare resources, patients from these regions typically present with advanced primary and nodal disease. In addition, the lack of basic transport networks restricts the ability for patients to commit to definitive courses of treatment, since such treatment often requires them to commute daily to the hospital for 6–7 weeks as per conventional fractionated NPC RT. The scarcity of machines and treating physicians further prolong waiting time for RT treatment, which is particularly pressing especially in patients who present with large bulky advanced disease.

In such patients, neoadjuvant chemotherapy is often proposed as an alternative treatment strategy while the patient awaits planning for radiotherapy. Nonetheless, it must be clarified that the use of induction chemotherapy for this approach counters the original intent of targeting occult metastasis (8). Chemotherapy also may not lead to ideal outcomes due to attendant issues for this group of patients, such as poor nutrition, poor social support, poor sanitary living conditions, as well as long commuting distances in case of any emergencies.

On this note, we therefore propose that GRID RT can be a useful treatment modality in this setting. Moreover, it has been shown that a relatively higher response rate (CR 23.3%, PR 60%) was observed in patients who received GRID RT in the head and neck area, as compared to that in other subsites (1). Firstly, the use of GRID allows us to deliver high dose palliative RT as a single fraction, compared with conventional open field RT. This is useful especially in cases with very large cervical nodal disease, allowing quick local and symptomatic control of the disease, sometimes with very dramatic results (1). Furthermore, GRID RT allows this dose to be given with minimal planning, thus facilitating rapid delivery, possibly even on the same day of consult. Such an arrangement will also cater for treatment of patients during off-hours in the evenings or during weekends. This is particularly attractive for patients since they obtain optimal relief of symptoms with a single session of treatment. If need be, GRID RT can be repeated with minimal toxicities (1).

In addition, the use of GRID RT for palliation does not preclude the patient receiving subsequent conventionally fractionated EBRT, with or without concurrent chemotherapy (4). As can be seen in the paper by Penagaricano *et al.* (4), radical concurrent chemo-RT after a single fraction of GRID resulted in good clinical and pathological response rates, as well as toxicity and complication rates not significantly different from concurrent chemo-RT alone.

Potential mechanisms underpinning tumour response with GRID

In the case of GRID therapy, we are looking at administration of hypo-fractionated doses per fraction of higher than 8 Gy. Hypo-fractionated RT may be defined as any fractionation schedule larger than conventional 1.8–2.2 Gy per fraction. In GRID, the doses used are usually in the region of 3–20 Gy daily fractions for 1–3 days, to a total of 8–20 Gy.

There is evidence to suggest that at such doses, the radiobiology may differ from the "classical" concepts of repair, re-assortment, re-oxygenation, and re-population. At such profoundly hypo-fractionated doses, molecular

pathways relating to ceramide-induced apoptosis (as a consequence of endothelial cell damage) and modulation of the adaptive immune response could be involved in determining the RT-response (9). In particular, the latter has been implicated as the dominant mechanism accountable for abscopal responses that have been observed with SBRT, especially in combination with new immunotherapeutic agents (10). As have been outlined by several reviews, including a paper by Prasanna *et al.* (3,10,11), we briefly summarise some of the points here.

Bystander/abscopal effects

Bystander effects refer to the phenomenon of cell killing in the shielded non-irradiated parts of the tumour and have been proposed as an important factor for the efficacy of GRID therapy. These effects have been largely attributed to cell-cell junctional communications facilitating the transfer of soluble mediators that are released by the irradiated cells, which could subsequently induce chromosomal damage in their adjacent un-irradiated neighbours (12-15). Abscopal effects describe distant responses in un-irradiated tumour lesions. The exact mechanism by which this occurs is uncertain, but the adaptive immune response has been repeatedly proposed (see "immune system activation"). In some studies, optimal response to GRID therapy has been correlated with increased TNF-α and ceramide production in the irradiated cells within the open areas of the GRID lattice (16-18).

Damage to endothelial cells

While lethal radiation-induced damage is induced following large doses of ionising radiation, this alone cannot account for such pronounced tumour regression with GRID therapy (19,20). Additional pathways are likely at play, including the activation of acid sphingomyelinase (ASMase) and ceramide generation in damaged endothelial cells (20-24). Evidence for this is derived from *in vivo* models demonstrating the lack of RT tumour killing efficacy following large ablative doses when ASMase was knocked out in mice implanted with fibrosarcomas and melanomas, and restoration of this pathway reversed the resistance phenotype (21). In addition, elevated sphingomyelinase activity and ceramide concentration were observed in the serum of patients undergoing GRID RT (17). Separately, elevated ASMase and low-density lipoprotein (LDL)-enriched ceramide were further shown to be predictive of response to GRID therapy (17).

In addition, the histo-morphological architecture of tumour endothelial cells is characterised by irregular morphology, large gap junctions, and a poorly supported basement membrane. Following high dose irradiation, these features promote the extravasation of plasma proteins causing an increase in the intra-tumoural fluid pressure and compression of capillary-like tumour blood vessels (25-27). A compilation of studies on radiation-induced vascular changes in tumours by Kim *et al.* also concluded that permanent severe vascular damage only occurs at doses of single 10 Gy and beyond, contrasting modest changes at doses of 5-10 Gy (28,29).

Immune system activation

Traditionally, RT has been regarded as immunosuppressive because lymphocytes being exquisitely radiosensitive are reduced in numbers after exposure to radiation. However, this may not be true in the case of GRID RT or SBRT. Single large doses to tumours have been shown to enhance T-cell priming within the $CD8^+$ T-lymphocyte subpopulation, leading to T-cell-mediated cytotoxicity against both the primary and metastatic tumour clones (19). The mechanism underpinning such a pronounced activation is unclear, but acute cytokine and tumour antigen release may be a factor (30,31); IFN-α/β produced by tumour-infiltrating myeloid cells enhances the cross-presentation of tumour antigen by dendritic cells and increased cytotoxic T-cell anti-tumour immunity (11,18). It has also been observed that conventionally-fractionated RT given after GRID radiation resulted in better response than conventional RT alone; this suggests that the acute responses leading to immune priming by GRID are possibly sustained, thereby enhancing the DNA damage-dependent tumour cell killing by conventional RT (3). Of note, persistent micronuclei formation beyond mitosis has been shown to trigger interferon signalling, which would further propose a linkage between both pathways (32). Other potential stimuli of the adaptive immune pathway include the release of tumour-specific antigens secondary to cell death, reactive oxygen species, interleukin (IL)-6, -8, tumour necrosis factor-α (TNF-α), and endoplasmic reticulum-derived proteins [i.e., calreticulin and danger-associated molecular patterns (DAMPs)] (33,34). Necrotic cells also release other danger signals, such as Hsp70 or HMGB1, which further

induce maturation of antigen presenting cells and promotes cross-presentation of tumour antigens (35,36). Collectively, these highlights the myriad of immune circuitry that could independently contribute to the better than expected clinical response that has been observed with GRID therapy.

Overcoming hypoxia

In the traditional 4Rs model of radiobiology, one of the purposes of fractionation is to overcome hypoxia and allow for re-oxygenation of tumour cells. Traditionally, hypoxic tumour cells have been known to be resistant to radiation and to many anticancer drugs. However, with the advent of SBRT, this high dose hypo-fractionated regimen has actually been shown to have greater tumour control than expected, possibly because such high doses are able to overcome the hypoxic radio-resistance of tumour cells (3). In addition, oxygen consumption would drastically diminish after the massive death of tumour cells through the abovementioned mechanisms, thus catering for the re-oxygenation of residual hypoxic tumour microenvironment (28). To add, the co-localisation of programmed death-ligand 1 (PD-L1) with hypoxia inducible factor-1α (HIF-1α) in recurrent NPC tissue also proposes the interdependency between the different compartments of the tumour microenvironment (37).

Reinvigorating GRID therapy—patient stratification and clinical studies

In recent years, there has also been great interest in immune modulation in oncologic treatment. The prognostic significance of peripheral blood neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) have been reported to correlate with the prognosis of several human cancers; for example, an elevated NLR has been reported to portend for inferior survival in NPC, after correction for clinical confounders (38-40). This raises the question of whether NLR can be used to select for patients more likely to respond favourably to immunologic modulation; and going a step further, if GRID RT can be utilised in immune activation to improve treatment responses.

From the therapeutic strategy angle, design of novel GRID-RT combinatorial regimes can be inferred from past and existing studies investigating the efficacies of sequential immunotherapy and RT. A small proof-of-concept clinical trial by Golden *et al.* examined the role of combinatorial granulocyte macrophage colony-stimulating factor (GM-CSF) and RT to stimulate dendritic cell (DC) maturation in 41 patients with metastatic solid tumours; abscopal out-of-field responses were observed in a-quarter of patients (41). Another trial by Grimaldi *et al.* examined patients (N=21) with advanced melanoma who were treated with sequential ipilimumab (anti-CTLA4-antibody) and RT. In the patients who responded locally, 84.6% of them also showed systemic responses (42). Judging the available evidence for immune stimulation post-RT, this prompts the question of whether GRID, with its simple single fraction administration could be employed for this purpose; we propose GRID as a form of immunotherapy induction, either alone (in the palliative setting) or prior to definitive conventionally fractionated RT.

Interestingly, gemcitabine, a common and affordable chemotherapeutic agent, has been shown to enhance cellular immunity through enhancing T-lymphocyte recall responses (43). Treatment of tumour-bearing mice with gemcitabine increased the cross-presentation of antigen to $CD8^+$ T-cells resulting in their reinvigoration and activation (44). This drug may also enhance immunogenicity indirectly by alleviating the suppression of the antitumor immune response (45-47). Therefore, using GRID RT, with or without additional methods of immunological stimulation, such as gemcitabine and other conventional chemotherapeutic agents, including progesterone analogues (47-55), or contemporary immunotherapy like checkpoint inhibitors, thus harbours the potential to be an exciting new area of research to be studied. If true, GRID RT presents a simple and cost-effective measure of harnessing the vast potential of immunotherapy in the targeting of cancers. This might also allow more centres to exploit this “cutting edge technology” of immunotherapy in an accessible and economical approach.

Conclusions

This paper is meant to stimulate discussion regarding the efficacy and applicability of this neglected modality of RT treatment; as well as hopefully to trigger new interest into researching the immunological anti-tumour effects of GRID RT.

In summary

(I) GRID RT is a modality that can be simply delivered in

a single fraction, with minimal planning time needed;

(II) It has been shown to be efficacious both as a single modality palliative treatment, as well as an initial/induction treatment before definitive radical treatment with conventionally fractionated EBRT, with or without chemotherapy;

(III) In head and neck cancers, the response of GRID RT has been shown to be especially robust. This makes it a suitable treatment to be used such as in the treatment of NPC, especially in medically underserved regions. GRID can both serve as a palliative treatment, to rapidly shrink large and symptomatic nodes, as well as a form of "induction", providing the patient some treatment and symptom relief, with a view to receiving more definitive treatment when resources become available;

(IV) There is evidence to show that with the large hypo-fractionated doses delivered in GRID RT, bystander effects, abscopal effects, as well as immunological anti-tumour activation can be triggered. While this has not been extensively researched, this area could be promising in terms of developing yet another usage for this treatment modality, with the added benefits or cost-effectiveness and simplicity of delivery, as compared to the other immunological agents being developed.

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