The Role of Program Project Grants in the Study of 3D Conformal Therapy, Dose Escalation and Motion Management

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PPGs in the Study of 3D Conformal Therapy, Dose Escalation + Motion Management

• What is a Program Project Grant?
• PPGs in Radiation Oncology
• Benefits of the PPG Mechanism: Examples from 3-D, Dose Escalation, + Motion Management
• Conclusions
Program Project Grant (PPG)

- A broad-based, multidisciplinary, often long-term research program with a specific major objective or theme addressed by a number of research projects
- A PPG has a central research focus, in contrast to the narrower thrust of traditional research projects
- Each project contributes to the common theme of the PPG, and is usually led by an established investigator
- Provides support for core components which facilitate the projects and overall research effort

Optimization of High Dose Conformal Therapy

Principal Investigator
BA Fraass

Project 1
Optimization
DL McShan

Project 2
Dosimetric Basis
BA Fraass

Project 3
Geom. Uncert.
RK Ten Haken

Project 4
Clinical Studies
TS Lawrence

Core A
Administration, Statistics
BA Fraass

Core B
Automated Tx Delivery
JMJ Balter

Core C
GA for Planning Deliv. Process
MK Martel

Core D
Computer Software
ML Kessler

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PPGs in Radiation Oncology

Protons at the Harvard Cyclotron (Suit):
• Proton Txs 1961-2002
• Fiducial-guided setup
• Sophisticated 3-D positioner
• 3-D Eye Plan – Goitein
• More Later...

Joint Center for Radiation Therapy (Bjarngard):
Computer-Controlled Tx
• First computer-controlled accelerator treatments
• Development of independent jaws, machine control, dynamic wedges
• Treatments that look similar to VMAT, tomotherapy

CN Coleman et al, IJROBP 47: 1357-69, 2000
Goitein, MGH
PPGs in Radiation Oncology
UCSF/Berkeley: Particle Therapy at the Bevalac (Castro):
- Tx with Carbon, Argon, etc
- Image registration
- DVH analysis
- Measuring organ motion
- Imaging dose deposition
- Lots of radiobiology
- ISAH, Isocentric Stereotactic Apparatus for Humans
- Lyman NTCP model

MSKCC: Develop New RT Techniques to Improve Local Control (Ling):
- Practical implementation of 3DCRT; MLC; computer-controlled Tx, DMLC IMRT
- Dose escalation: nasopharynx, prostate, lung
- TCP/NTCP + biophysical models, optimization
- Uncertainties + Tx error, DIBH, motion, gating

UM: Optimization of High Dose Conformal Therapy (Fraass-TenHaken):
- 3D Planning + Tx, Optimization, SMLC IMRT, Motion, Fncrt Imaging
- Dose Escalation: Liver, Lung, Prostate, Brain
- H/N Parotid-Sparing, pharangeal constrictors, SIB IMRT
- PET, SPECT, MR Fncrt. imaging for response-driven adaptation
PPGs in Radiation Oncology

VCU-MCV: Image Guided Adaptive Radiotherapy (Williamson):
- Interfraction motion effects (prostate, cervix)
- 4D RT and tracking, in lung
- Probabilistic treatment planning
- Deformable image registration and dose mapping

Some other technically-inclined RT PPGs:
- MD Anderson: radiobiology
- U Wisconsin (Mehta): Tomotherapy
- MGH-MD Anderson: Proton Therapy
- MSKCC: Tumor Hypoxia Imaging (Ling) 2006-2012

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Advantages of the PPG Mechanism
Continuity which allows long-running projects to follow promising leads

Protocol Enabled by:
- Many years of diffusion
- MR, FDG PET, C11
- Methionine PET, image registration, inverse planned IMRT, correction for fractionation, functional imaging analysis tool (FIAT)

Advantages of the PPG Mechanism
Integrated development, testing and use of new techniques which allow more sophisticated clinical studies

Example:
Liver and lung dose escalation using Iso-NTCP-based protocols

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Technical improvements (e.g. motion control, ABC, IMRT, etc) move plan along dose-vol curve, “w/in protocol”

Dose esc. depends on the normal tissue dose-vol-toxicity relationship, not any particular technology, so new techniques are allowed!

Typical Paradigm for New Technology Development?

New Stuff

Make New Stuff

Robust enough for routine clinical use

Try it to see if it works

Is it better?

Do Clinical Study

Typical Paradigm for Clinical Development?

Evaluate Clinical Results

(Toxicity, Control)

Clinical Study:

Improved Results?

Determine new needs

However, this takes way too long!

Make New Stuff

Robust enough for routine clinical use

Identify technical functionality needed

New Stuff
Advantages of the PPG Mechanism
Integrated clinical and technical development and testing

Within the PPG mechanism, there is enough freedom so:
1. Clinical and technical timelines can run concurrently
2. One can work to predict technological needs many years ahead
3. It is possible to get the clinical data necessary to effectively use the new stuff
4. This freedom allows us to design trials to study clinical changes which are made possible by a new technology, not the technology itself

Advantages of the PPG Mechanism
Support for infrastructure and developments necessary for clinical implementation of new ideas + technology

PPG cores provide shared support for the research, and also partial funding for clinical implementation
For example, Cores in the MSKCC PPG included work on:
• The SPIN (simulation/portal image network) project
• The dosimetry of dynamic MLC for photons and electrons
• Advanced planning tools for computer-aided optimization

Advantages of the PPG Mechanism
Supports broad collaborations and multidisciplinary research efforts

UM PPG 2005

MSKCC PPG 2002-07
Advantages of the PPG Mechanism

Phase I/II studies performed by PPGs have a harmony, synergy + synchrony that feed big clinical trial mechanisms

The large NRG/RTOG trials that have a significant effect on standard practice are often based on the early phase I/II studies that PPGs often make possible:

- **1990s**: Phase I/II Parotid-Sparing (UM PPG)
- **1990s**: GBM Dose Escalation, UM PPG
- **2000s**: Lung Dose Esc, UM PPG
- **2001-2005**: RTOG H0022 (IMRT for Oropharyngeal CA)
- **now**: NRG-BN001, Hypofx'd Dose Escalated IMRT vs Conventional Irrad (with Tem)
- **now**: RTOG 1106, Adapt Lung Dose based on PET after Tx 18-21

Advantages of the PPG Mechanism

Flexibility which allows studies to evolve from technology-enabled trials to advanced response-outcome trials leading to adaptive (precision medicine) trials

Advantages of the PPG Mechanism

The "PPG created the framework for high level intra-departmental collaboration --- it . . . got everyone going in the same direction" – J Seibers (VCU-MCV)
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Conclusions

- PPGs provide relatively unique and major funding for multi-faceted, interdisciplinary projects which support complex + long-term clinical research
- The coordinated clinical and technical development and testing strategies allowed by the PPG funding have been (at least partly) responsible for a wide variety of clinical advances – in 3-D, IMRT, dose escalation, sophisticated conformal therapy, adaptive therapy, 4-D, motion management, and many other advances that have become the standard of practice in the field

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