Real World Evidence in the Treatment of Ovarian Cancer

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Queen’s University
Outline

• What is “real world evidence” (RWE) and how can it shape policy and practice?
• In ovarian cancer, is there RWE that new treatments are affecting outcomes?
• Does OVCA population level data support the impact of treatment on outcomes?
Novel Treatments in Ovarian Cancer Based on RCT Evidence

Randomized Clinical Trial Results

Regulatory Agency Review Approval

Policy Approval for Formularies & Guidelines

Practitioner/Patient discussions Preferences and decisions
What is **Real World Evidence**?

- Population based observational research
- Uses data derived from heterogeneous sets of patients in real life practice settings.
- Can address questions such as:
  - *Utilization and uptake* of treatments, procedures into practice
  - Outcomes
    - *New Safety information*
    - *Population Effectiveness*
    - *Health economics*
- Usually uses administrative data (e.g. cancer registry, physician billings, prescriptions, insurance claims etc.)
- *Complementary role to RCTs*
Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence

C M Booth*1 and I F Tannock2

1Division of Cancer Care and Epidemiology, Queen’s University Cancer Research Institute, 10 Stuart Street, Kingston, ON K7L 5PG, Canada and 2Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada
## Strengths

<table>
<thead>
<tr>
<th>Randomised controlled trials</th>
<th>Pop’n-based observational studies</th>
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<tbody>
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<td>• Excellent <em>internal</em> validity</td>
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<td>• Provide precise measures of <em>efficacy</em> and <em>acute toxicity</em> of new therapies under ideal conditions</td>
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<td>• Because of randomisation, measurement of effect size is less prone to bias</td>
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<td>• Can evaluate prognostic and predictive properties of new biomarkers and therapies</td>
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<td>• Mechanism whereby new (and potentially toxic) treatments can be carefully studied in centres of excellence</td>
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<td>• Good <em>external</em> validity</td>
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<td>• Provide insight into delivery of care in routine practice to all patients, including elderly and those with comorbidity</td>
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<td>• Can provide evidence of <em>effectiveness</em> of new therapies in the general population</td>
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<td>• Large samples provide the opportunity to study rare diseases for which RCTs are not possible</td>
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<td>• Can provide insight into short- and long-term toxicity in routine practice</td>
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# Limitations

## Randomised controlled trials
- Limited *external* validity
- Provide evidence of *efficacy* but *not about effectiveness* (benefit to patients in routine practice)
- **Applicability to clinical practice can be limited:**
  - Pts/ MDs in RCTs are different from those in practice
  - Elderly & pts with comorbidity are under-represented in RCTs
  - May use a surrogate endpoint
  - Limited ability to detect rare and chronic toxicities

## Pop’n-based observational studies
- Limited *internal* validity: may be difficult to separate effects of a new treatment from other factors
- Pop’n-level databases often do not include detail re: comorbidity, performance status, etc.
- **Identification of comparative benefit in these studies prone to multiple biases. e.g.:**
  - confounding by indication for a given treatment
  - concurrent changes in practice and/or disease biology
RWE can influence policy and practice

• Poor utilization of effective treatments → may make practitioners and policy makers identify (and resolve) barriers, KT etc.

• Significant new safety concerns → may lead to changes in practice/indications

• Less than anticipated effectiveness → reduction in prescription/utilization
For Ovarian Cancer:

Does “real world” evidence show impact of last 30 years of innovations through RCTs?

• Main outcome of interest is *effectiveness*

• Two sources of data reviewed:
  – Population studies about:
    • *Uptake* of specific interventions/treatments
    • *Effectiveness* of specific interventions/treatments
  – Cancer Population Registry trends on *incidence, survival and mortality*
Interventions with *Potential Impact* on OVCA Incidence, Survival & Mortality Rates

- **Prevent**
  - OC pills

- **Treat**
  - Bev’mab
  - IP chemo
  - Gem. L-Dox
  - HRT stops
  - Taxane(s)
  - Platinum(s)
Population Studies

• Few to be found

• Literature: studies addressing both use of guideline based therapy and comparative outcomes
Impact of National Cancer Institute Comprehensive Cancer Centers on Ovarian Cancer Treatment and Survival

Robert E Bristow, MD, MBA, FACS, Jenny Chang, MPH, Argyrios Ziogas, PhD, Belinda Campos, PhD, Leo R Chavez, PhD, and Hoda Anton-Culver, PhD
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology (Bristow), and the Department of Epidemiology (Chang, Ziogas, Anton-Culver), University of California, Irvine - School of Medicine; and the University of California, Irvine - School of Social Sciences (Campos, Chavez), Irvine CA

- 9,933 OVCA pts – 8.1% treated at NCI-CCCs
- Overall, 35.7% received NCCN guideline adherent surgery + chemo (45.5% in CCC and 34.7% in non-CCC hospitals)
- Greater adherence to chemo (62%) than surgical (51.2%) guidelines
• **Bottom Line**— This USA population study shows uptake/use of evidence based ovarian cancer treatments is low and varies by place of treatment.

In a multivariate analysis, hospital of treatment and SES were independent predictors of OS (p < .0001); OS better in CCC patients.

• Unclear if related to guideline compliance or other factors that might differentiate pts.
• 823 stage III OVCA pts treated at 6 comprehensive cancer centre network sites

• Tracked use of IP chemo from 2003-2012

• Compared OS and toxicity outcomes in propensity score matched sample (n=402)
Fig 3. Overall survival with propensity score–matched sample for National Comprehensive Cancer Network patients with optimally cytoreduced, stage III ovarian cancer by first-line chemotherapy administration with intraperitoneal or intravenous (IP/IV) chemotherapy, 2006 to 2012.
Neoadjuvant Chemotherapy (NACT) vs. Primary Cytoreductive Surgery (PCS)

- RCTs of patients suitable for either NACT or PCS suggest NACT non-inferior\(^1,2\)

- In practice, guidelines favour offering PCS to “fit” pts if optimal debulking likely achievable and NACT to others.

- e.g., ASCO guidelines\(^3\) “Women who have a high perioperative risk profile or a low likelihood of achieving cytoreduction to 1 cm (ideally to no visible disease) should receive NACT”

- Population studies will likely reflect the fact that poorer patients are selected for NACT than PCS

1. Vergote I, NEJM 2010
Population study:
- 22,962 pts age <70; comorbidity index 0. 3,126 had NACT
- No info on what led to selection of NACT
- ~15% of PCS pts never got chemo
- ~26% of NACT pts never got surgery

In propensity score matched cohorts of 2935 patients:
- OS longer in PCS group (37.3 mo vs. 32.1 mo., p <.001)
- BUT differences would have been erased if there were excess of PS 1-2 pts in NACT group (60% vs 50%). Data on PS not available.
Seeking Evidence of Impact of OVCA Treatment

Population Survival and Mortality Trends
Effects of Screening Programs, Changes in Risk Factors, Treatments on Incidence and Mortality Trends

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<td><strong>Effective (curative) treatment</strong></td>
<td>↑ <em>sometimes (may depend on magnitude of effect and proportion of population affected)</em></td>
<td>↓</td>
<td>Adjuvant Breast Testicular Ca</td>
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Ovarian Cancer: Trends in Incidence, Survival, Mortality

- **Mortality:**
  - Age standardized mortality rates are **FALLING** in USA, Europe, Canada and elsewhere
Canada - OVCA Age Standardized Mortality Rate decreased by 0.7% per year
Global trends and prediction of cancer mortality

M. Malvezzi\textsuperscript{1,2}, G. Carioli\textsuperscript{2}, T. Rodriguez

\textsuperscript{1}Department of Epidemiology, IRCCS-Istituto di Ricerche Farmaco, Università degli Studi di Milano, Milan, Italy; \textsuperscript{2}Laboratorio Unificato

![Graph showing death rate per 100,000 from 1970 to 2010 for different regions: USA, EU, Japan.](image-url)
Is improvement in OVCA Mortality related to better treatment, reduced incidence, or both?

- **Incidence:**
  - Overall incidence rates appear to be **FALLING** in many jurisdictions
  - Likely related to protective effect of OC use (from 1960s-70s) and also reduction in use of post-menopausal HRT (from 2001 onwards)
Canada – Trends in Incidence & Mortality

OVCA age standardized
Rate decreased by 0.8% per year
Since 1992

OVCA age standardized
Rate decreased by 0.7% per year
since 1974
Accelerated decline in incidence rate of OVCA after release of WHI results

- In 2001, WHI results became known.
- HRT use fell quickly and in parallel, rate of decline in OVCA also changed from 0.8% per year to 2.4% per year

(Yang HP. J Clin Oncol 2013)


Brigitte Trétarre a,*, Florence Molinié b, Anne-Sophie Woronoff c, Nadine Bossard d, Faiza Bessaoud a, Emilie Merrer e, Pascale Grosclaude f, Anne-Valérie Guizard g, Patricia Delafosse h, Simona Bara i, Michel Velten j, Bénédicte Lapôte-Ledoux k, Karine Ligier l, Nathalie Léone m, Patrick Arveux n, Zoé Uhry o d

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>Mortality</th>
<th>AAPC (%)</th>
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<tbody>
<tr>
<td>1980</td>
<td>3492</td>
<td>9.1</td>
<td>−0.6</td>
</tr>
<tr>
<td>1990</td>
<td>3899</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>4284</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>4489</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>4592</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>4615</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>1980–2012</td>
<td>4615</td>
<td>3140</td>
<td></td>
</tr>
<tr>
<td>2005–2012</td>
<td>3140</td>
<td>3140</td>
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N, number of cases; ASRW, age-standardized rates on the world population per 100,000 women; AAPC, average annual percentage change.
Incidence rates vary greatly

• While incidence rates for OVCA are variable, *TIME trends show that incidence rates are falling in many countries.*

• Unclear if incidence rate decline alone can explain mortality rate decline – but it likely plays an important role
What about changes in survival?

• In the absence of screening programs (which can yield lead time biases), *improvements in relative survival or cancer specific survival* are most plausibly related to *treatment effect*.

• Trends show 5-year relative survival in OVCA is *increasing*
New Cases, Deaths and 5-Year Relative Survival

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<tr>
<td>5-Year Relative Survival</td>
<td>33.7%</td>
<td>38.2%</td>
<td>38.7%</td>
<td>40.4%</td>
<td>42.2%</td>
<td>43.0%</td>
<td>44.3%</td>
<td>46.2%</td>
</tr>
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Summary

• In Cancer research - the goal of *novel treatments and interventions* is to improve population outcomes

• RWE can help determine if there is uptake of these and whether the anticipated benefits are being (safely) realized.

• **There are few RWE studies of specific treatments in OVCA**
  – 1 paper of IP suggests modest uptake but OS impact
  – NACT RWE studies confounded by patient selection

• **Registry level data** show falling mortality rates over last 4 decades – in parallel to falling incidence rates. Treatment effects may also be adding to this but cannot be isolated.

• Progress is slow however – more work to be done in prevention, screening **AND** treatment.