Unmet needs in high-risk non-muscle invasive and localized muscle invasive bladder cancer: a systematic literature review in the French setting

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CONTEXT & OBJECTIVE

Bladder cancer ranks second among urological cancers in France, with an annual incidence of 14,062 new cases and more than 5,335 deaths.[1] The recurrence and progression rates are high for intermediate/high-risk non-muscle invasive bladder cancer (IR/HR NMIBC) and muscle invasive bladder cancer (MIBC). While alternatives to radical cystectomy (RC) are under development, there are still unmet patient needs especially for BCG unresponsive patients and for those ineligible for RC.

The objective was to review current literature to specify the unmet needs in France for BCG unresponsive patients and for those ineligibles for RC.

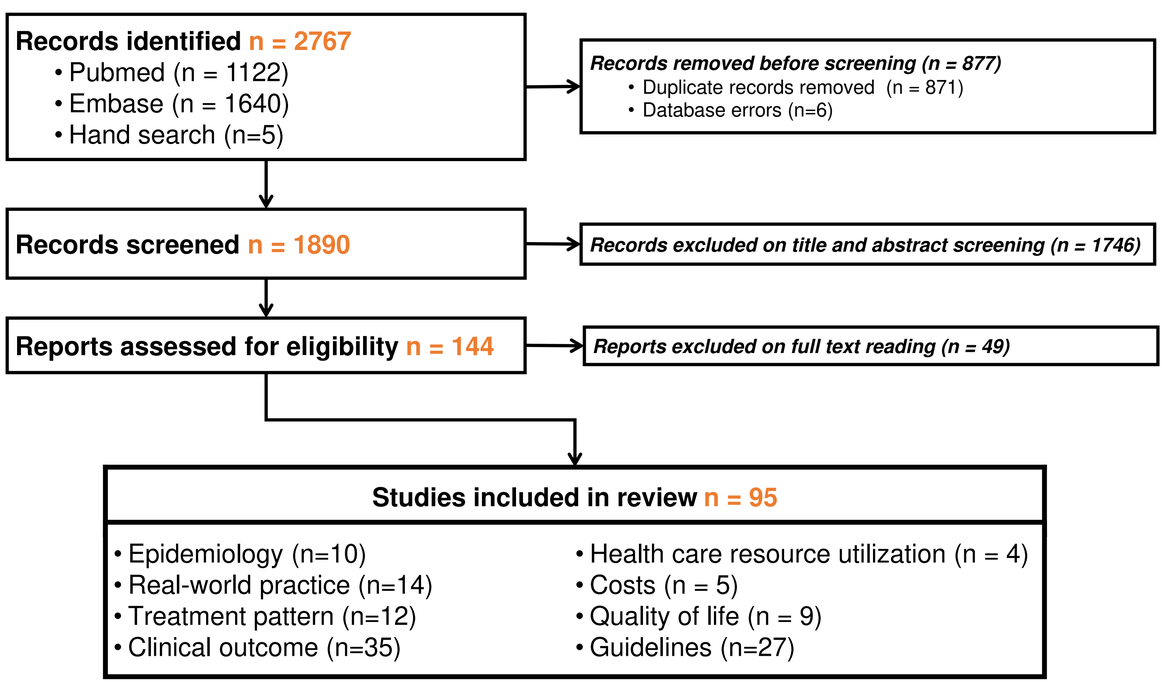
METHOD

- Systematic review of the literature on guidelines, epidemiology, disease burden, and real-life management of IR/HR NMIBC and localized MIBC in a French setting.
- We included all articles, congress abstracts, and reports from the grey literature, published in English or French, between 2014 and 2024, using PubMed and Embase search engines.
- All identified studies are subject to a 4-step screening process in accordance with the PRISMA framework: identification, screening, eligibility and inclusion.
- Relevant data are extracted from each selected study and then critically analyzed and synthesized.

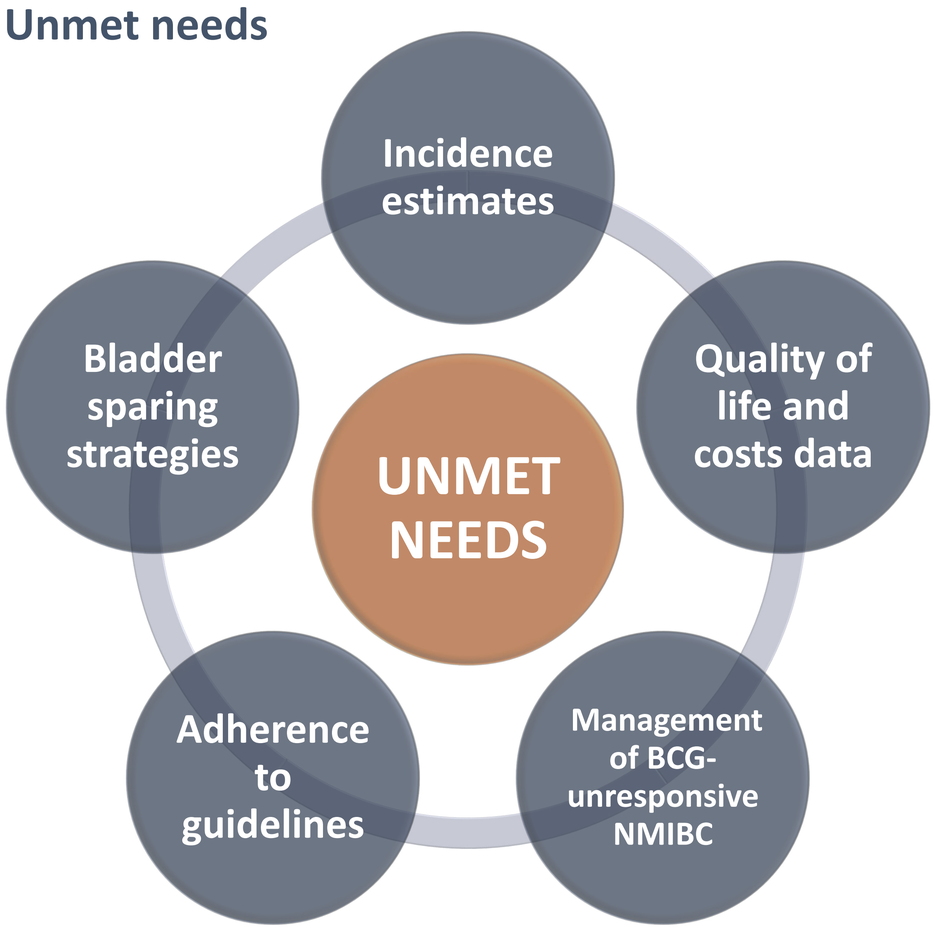
RESULTS

A. Study selection

We identified a total of **2767 records** and included **95 studies for review**. The PRISMA flowchart is presented below



B. Unmet needs



There is a need for **better estimates of the incidence of NMIBC, particularly patients at high risk of recurrence.**

The incidence of NMIBC, particularly patients at high risk of recurrence, is systematically underestimated in national reference epidemiological studies.[2,3] **Historically,** bladder tumors that do not infiltrate the basement membrane (pTa, pTis) **tumors were not registered by the local registry.** Thus, registries need to review their practice following clinician who grouped them together with those that infiltrate it without reaching the bladder muscle (pT1) under the term NMIBC (as opposed to MIBC of stage at least equal to pT2.

There is a need to **identify a subset of patients who are good candidates for bladder-preserving strategies to guide treatment decisions and improve patient outcomes**.

- Bladder-preserving therapy is **not yet an international standard treatment in routine practice**, particularly for younger patients. [4]
- **Real-world data on patient's management is scarce**, especially regarding bladder preservation strategies for HR-NMIBC BCG-unresponsive patients.
- We found very limited information and guidelines available on the **characteristics of patients who are ineligible or refuse RC**.
- **Predictive factors** that guide treatment decisions for bladder preservation with trimodal treatment (TMT) **are lacking, especially for older patients with comorbidities**. **The estimated risk of local recurrence after TMT varies widely in the literature, ranging from 10% to 40%. Furthermore, salvage cystectomy is associated with significant morbidity and mortality**. [4-9]
- There is a **lack of randomized controlled trial between RC and TMT** series with only indirect comparison biased in terms of patient selection and tumor staging. [4]

There is a need for **treatment preventing disease progression for BCG-unresponsive NMIBC.**

- **Very high-risk tumors who fail BCG** are at **risk of undertreatment** and **potential progression to MIBC** despite treatment with intravesical chemotherapy, with the possibility of rapid lymph node involvement and/or metastatic spread due to the aggressive profile of this type of tumors.[14]
- **Identifying predictive factors of progression after BCG** failure is crucial for guiding treatment decisions and improving patient outcomes.[15]
- **There is a lack of alternative to existing intravesical therapies** that can achieve complete response rates and prevent disease progression **for patients who fail BCG**.[15]

There is a need for **reliable data on quality of life, costs and resources use in France**

- **Efficiency model of nivolumab in bladder cancer assessed by French HTA presented a major overall uncertainty**
  - Data insufficient to ensure transposability from trial to French population
  - Insufficient exploration of uncertainty surrounding utility scores in post-recurrence health states
- **EQ-5D data are missing in the French cohort COBLAnCE** (6 years follow-up).[16-18]
- **HCRU data were identified,** mainly for inpatients and grouping **MIBC and NMIBC**).[19-21]
- **Costs data are available by subgroup of NMIBC** (IR/HR).[22]

There is a need for **more effective dissemination and implementation of clinical guidelines.**

- **Adherence to national and international guidelines is poor**. [10-13]
- In France, **only 67% of urologists self-assessed as knowing or well-knowing the recommendations** of the French Association of Urology regarding instillation of intravesical chemotherapy.[10] Although most European physicians claim to apply the European Association of Urology guidelines, **adherence to them is low in daily practice**.[11]
- Adherence to the guidelines for the initial treatment of NMIBC is poor, particularly for intermediate-risk, high-risk, and very high-risk patients. **Addressing the reasons for non-adherence**, such as the urologist's decision or the patient's condition might improve the rate of adherence to NMIBC guidelines.[12,13]

CONCLUSION

Further studies are needed in France to address the data gaps identified in this systematic literature review.

1. *Lapôtre-Ledoux et al. BEH 2023.*
2. *Neuzillet et al. BJU Int 2023.*
3. *Palou et al. World J Urol 2018.*
4. *Fabiano et al. Acta Oncol 2021.*
5. *Messaoud et al. Prog Urol 2022.*
6. *Gontero et al. Eur Urol 2015.*
7. *Reignier et al. World J Urol 2023.*
8. *Simon et al. PLoS One 2019.*
9. *Alati et al. J Geriatr Oncol 2022.*
10. *Jubber et al. Eur Urol 2023.*
11. *Neuzillet et al. Prog Urol 2016.*
12. *Jeglinschi et al. Prog Urol 2020.*
13. *Surlemont et al. Prog Urol 2021.*
14. *Doisy et al. Int J Hyperthermia 2021.*
15. *Pignot et al. World J Urol 2023.*
16. *Campagna et al. Prog Urol 2022.*
17. *Roupret et al. 2015*
18. *Benhamou et al. BMC Cancer 2016.*
19. *Grobet jeandin et al. World J Urol 2022.*
20. *Mjaess et al. Eur J Surg Oncol 2023.*
21. *Tostivint et al. Prog Urol 2023.*
22. *Ourfali et al. Eur Urol Focus 2021.*

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